Result Page

Pyrimidin connections, methods to their preparation, pharmaceutical preparations containing these connections, as well as their therapeutic
Use.

The present invention concerns < RTI ID=1.1> 2 (Pyrimidinylamino) - 1,3-< /RTI> < RTI ID=1.2> diaza-2-cycloalken-Verbindungen, < /RTI> in particular the formula
EMI1.1
where Py if necessary substituted 4 connected by a carbon atom with the nitrogen atom - or 5-Pyrimidinylrest represents, g 1 and R2 independently hydrogen, Niederalkyl or Niederalkenyl mean, and, their tautomeren bonds and salts, as well as method stands for alkene for Niederalkylen, which separates the two nitrogen atoms by 2 to 4 carbon atoms to their preparation, the connections of the formula I and their salts as pharmakologisch active connections, pharmaceutical preparations containing such connections, and the use of the new connections as pharmakologisch effective materials, as well as to the preparation from pharmaceutical preparations.

The Pyrimidinylrest Py represents 4 - or to 5, preferably a 4-Pyrimidinylrest, e.g. Niederalkyl, Cycloalkyl, Hydroxy, Niederalkoxy, Niederalkylthio, halogen, tri fluorine methyl, Niederalkylsulfonyl, if necessary substituted Phenyl or Phenoxy, and/or if necessary substituted Amino as substituents contained can.

In connection with the available description with ?down? designated remainders and connections contain preferably up to 7, mainly up to 4 carbon atoms.

Niederalkyl stands, e.g. in particular for methyl, as well as for ethyl, n-Propyl, Isopropyl, n-butyl, Isobutyl or third. - Butyl, as well as n-Pentyl, Neopentyl, n-Hexyl or n-Heptyl.

Niederalkenyl e.g. stands. in particular for allyl, a 1, 2oder 3-Methylallylgruppe.

Niederalkoxy e.g. is. in addition, primarily Methoxy, can < RTI ID=2.1> Aethoxy, < /RTI> N-Propyloxy, Isopropyloxy or n-Butyloxy, furthermore n-Pentyloxy < RTI ID=2.2> sen.< /RTI>

Niederalkylthio is in particular Methylthio, furthermore also Aethylthio, Isopropylthio, n-Propylthio or also a straight or branched Butylthio.

Nideralkylsulfonyl e.g. is. Methyl sulphonyl, ethyl sulphonyl, n-Propylsulfonyl or Isopropylsulfonyl.

A cycloalkyl residue is primarily a Cycloalkylgruppe with 3-6 ring carbon atoms and e.g. is. a Cyclopropyl, a Cyclobutyl, a Cyclopentyl or a group of cyclohexyls.

Halogen is in particular halogen with atomic number up to 35 and stands mainly for chlorine, furthermore for fluorines or bromine.

top A if necessary substituted phenyl or Phenoxyrest can by one, two or three equal or different substituents substituted to be. Such substituents e.g. are. Niederalkyl, if necessary functional modified Hydroxy or Mercapto, like ether width unit Hydroxy, e.g. Niederalkoxy, Niederalkenyloxy or Niederalkylendioxy, furthermore Niederalkylthio, or halogen, tri fluorine methyl, Nitro, Amino including substituted Amino, e.g. Niederalkylamino or Diniederalkylamino, if necessary functional modified Carboxy, like ester width unit Carboxy, e.g. Niederalkoxycarbonyl.

Niederalkenyloxy e.g. is. primarily Vinyloxy or Allyloxy.

If necessary substituted Amino can be by Niederalkyl or substituted Phenyl substituted if necessary and e.g. is.

Niederalkylamino or Diniederalkylamino, like Methylamino, Aethylamino, Dimethylamino or Diäthylamino, Phenylamino, 4-Methoxy-phenylamino or < RTI ID=3.1> 4-Chlor-phenylamino.< /RTI> It can be also through, if necessary oxygen, sulphur or if necessary Niederalkyl containing nitrogen as ring member exhibiting Niederalkylen substituted and e.g. Niederalkylenamino, e.g. Pyrrolidino or Piperidino, Oxaniederalkylenamino, < RTI ID=3.2> e.g. < /RTI> Morpholino, < RTI ID=3.3> Thianiederalkylenamino. e.g. < /RTI>

Thiomorpholino or Azaniederalkylenamino, e.g. Piperazino or 4-Niederalkyl-piperazino, like 4-Methyl-piperazino, represent. Substituted Amino knows also Acylamino, like Niederalkanoylamino, e.g.

Acetylamino or Propionylamino, Niederalkoxycarbonylamino, e.g.

Methoxycarbonylamino or Aethoxycarbonylamino, or if necessary by Niederalkyl substituted Ureido, e.g. Ureido, 3-Methylureido or 3,3-Dimethylureido, < RTI ID=3.4> sen.< /RTI>

A Niederalkylengruppe alkene is preferably normal Niederalkylen and stands mainly for ethylen, in addition, as well as for 1,3, branched Niederalkylen knows propylene or 1,4-Butylen, as 1,2-Propylen, 2-Methyl-1,2-propylen or 2,3-Butylen

to represent.

Salts of connections of the above formula I are acidic addition salts, pharmaceutical, non-toxic acidic addition salts with inorganic acids, z.3, usable in particular. Hydrochloric acid, hydrobromic acid, sulphuric acid or phosphoric acids, or with organic acids, like appropriate carboxylic acids, e.g. Acetic acid, propionic acid, glycol-acidic, succinic acid, maleic acid, < RTI ID=4.1> Hydroxymalein < /RTI> acidic, methyl maleic acid, fumaric acid, apple-acidic, tartaric acid, citric acid, benzoic acid, Zimtsäure, almond-acidic, salicylic acid, 4-Aminosalicylsäure, 2-Phenoxybenzoesäure, 2-Acetoxy-benzoesäure, Embonsäure, nicotinic acid or isonicotinic acid, or sulfonic acids, e.g. methane-sulfone-acidic, ethane-sulfone-acidic, < RTI ID=4.2> 2-Hydroxyäthansulfonsäure, < /RTI> < RTI ID=4.3> ethane l, 2-< /RTI> disulfonsäure, benzene sulfonic acid, 4-Methyl-benzol-sulfonsäure or Naphthalin-2-sulfonsäure.

Due to the close relationship between the new connections in free form and in form of their salts, inclusive also such acidic addition salts, those as intermediate products, e.g. with the purification of the new connections or to their identification to be used know, are preceding and in the following by the free connections sense and appropriately if necessary also the appropriate salts to be understood.

The bonds of the present invention exhibit valuable properties, mainly pharmakologische effects. Thus they show hypotensive and antihypertensive effects, which at anaesthesia ores trolleys in sockets starting from approximately 0.1 mg/kg with intravenous administration (whereby also the pressorischen effects of adrenalin and Noradrenalin are antagonisiert) and renal hypertonischen rats in sockets starting from approximately 10 it < itself on; RTI ID=4.4> mg/kg/Ilag< /RTI> with oral administration to prove leave. Furthermore the connections according to invention work on < RTI ID=4.5> heart < /RTI> activity, which < on the basis at the insulated guinea pig forecourt with concentrations of 100; RTI ID=4.6> pg/ml< /RTI> determined positively inotropic and in concentrations starting from 10 < RTI ID=4.7> jg/ml< /RTI> determined negative chronotropic effects to be proven knows. The connections of the formula I point a favorable therapeutic index, i.e. a favorable Relationship between effective and toxic dose, up. The bonds of the present invention become therefore as pharmakologisch effective junctions, mainly as Antihypertensiva the treatment of increased blood pressure, e.g. in connection with essentiel < RTI ID=5.1> ler< /RTI> Hypertonia, and as Kardiotonika uses.

The invention relates to or different substituents of the group Niederalkyl, Hydroxy, Niederalkoxy, Niederalkylthio, halogen, tri fluorine methyl, Niederalkylsulfonyl, amine, if necessary by Niederalkyl, equal mainly to connections of the formula I, worinPy for if necessary by one, two or three Niederalkoxy, Hydroxy, Amino, Niederalkylamino, Diniederalkylamino or halogen substituted Phenyl, Phenoxy or Phenylamino, Niederalkylamino, Diniederalkylamino, Pyrrolidino, Piperidino, Morpholino, Thiomorpholino, Niederalkanoylamino, < RTI ID=5.2> Niederalkoxycarbonylamino, < /RTI> Ureido, 3-Niederalkylureido and 3,3-Diniederalkylureido substituted, over a carbon atom with the nitrogen atom connected 4 - or 5-Pyrimidinyl, in particular 4-Pyrimidinyl stands, < RTI ID=5.3> R1< /RTI> and R2 independently hydrogen, Niederalkyl or Niederalkenyl mean, and for alkene for Niederalkylen it stands which separates the two nitrogen atoms by 2 to 4 carbon atoms, whereby with ?down? designated remainders up to 4 carbon atoms contain, their tautomeren connections and salts, pharmaceutical, non-toxic acidic addition salts usable in particular from it.

The invention relates to mainly connections of the formula I, where Py for if necessary equal to the group of Niederalkyl, Niederalkoxy, Phenyl, Amino, Niederalkylamino, Diniederalkylamino or Morpholino and/or halogen substituted, over a carbon atom with the nitrogen atom connected 4 by one, two or three or different substituents - or 5-Pyrimidinyl, in particular 4-Pyrimidinyl stands, g 1 hydrogen or Niederalkyl and R2 hydrogen or Niederalkyl represent, and for alkene for Niederalkylen stands, which separates the two nitrogen atoms by 2 to 3 carbon atoms, whereby ?down? carbon atom containing, and halogen named remainders up to 4 Atomic weight up to 35 exhibits, and salts, pharmaceutical, non-toxic acidic addition salts of, it usable in particular.

The invention relates to in particular connections of the formula
EMI6.1
where Alk' for Niederalkylen with up to 4 carbon atoms, which separates the two nitrogen atoms by 2 to 3 carbon atoms, < in particular for; RTI ID=6.1> Methylen< /RTI> , and each of the remainders of R3, R4 stands and < RTI ID=6.2> R; < /RTI> Hydrogen, Niederalkyl with up to 4 carbon atoms, < RTI ID=6.3> z+B.< /RTI> Methyl, or Niederalkoxy with up to 4 carbon atoms, e.g. Methoxy, or halogen, like e.g. Chlorine or bromine, or Diniederalkylamino, like e.g. Dimethylamino or Diäthylamino, Morpholino or Phenyl, meant, whereby preferably at least one of the remainders of R3, R4 and R5, preferably however two of it, is different from hydrogen, mean, and salts, pharmaceutical, non-toxic acidic addition salts of, it usable in particular.

The invention relates to in particular connections of the formula
EMI6.2
< RTI ID=6.4> where R3 and R4 independently for hydrogen, Niederalkyl
3 4< /RTI> with up to 4 carbon atoms, e.g. Methyl, or Niederalkoxy with up to 4 carbon atoms, e.g. Methoxy, halogen, e.g. Chlorine, Diniederalkylamino, e.g. Dimethylamino stand, whereby preferably both of the remainders < RTI ID=6.5> R3< /RTI> and < RTI ID=6.6> R4< /RTI> from hydrogen differently are and primarily Niederalkyl, e.g. Methyl, Niederalkoxy, e.g. Methoxy, halogen, e.g. Chlorine or Diniederalkylamino, e.g. Dimethylamino mean, and for 2 and for 1 stands for n mainly, and salts, pharmaceutical, non-toxic acidic addition salts of, it usable in particular.

The invention relates to mainly the connections of the formula I and salts, pharmaceutical, non-toxic acidic addition salts of, it usable described in the examples, in particular.

The bonds of the present invention can be manufactured after actually well-known methods, e.g. by a connection of the formula Py-x < RTI ID=7.1> (IV) < /RTI> oder ein Salz davon mit einer Verbindung der Formel
EMI7.1
or a salt of the fact it converts where one of the remainders of X and Y an amino group of the formula < RTI ID=7.2> -N (R2) - H< /RTI> < RTI ID=7.3> (VI) < /RTI> represents, and the other one one on the reaction conditions as well as hydrogen < RTI ID=7.4> gap < off; /RTI> cash group means, and, if desired, a received connection of the formula < RTI ID=7.5> r< /RTI> into another bond I of the formula transfers, and/or, if desired, a received salt into the free connection or into another salt transfers, and/or, if desired, a received free connection transfers into a salt, and/or, if

desired, a received mixture of isomers in individual isomers isolates.

A group of X split offable together with hydrogen and/or. Y e.g. is. primarily a free or preferably verätherte < RTI ID=7.6> Hercapto < /RTI> group, furthermore a reactive, functional modified hydroxy group or the Nitroaminogruppe. A verätherte Mercaptogruppe is mainly one by a if necessary substituted hydrocarbon remainder, in particular an aliphatic character, verätherte Mercaptogruppe. It places primarily Niederalkylthio, e.g.

Methylthio, Aethylthio or Butylthio or < RTI ID=7.7> Phenylniederalkylthio, < /RTI> e.g. Benzylthio. A reactive, functional modified hydroxy group is an appropriate verätherte or veresterte Hydroxy group. Such is among other things Niederalkoxy, e.g. < RTI ID=8.1> ethoxy, < /RTI> or halogen, e.g. Chlorine or bromine, or Niederalkylsulfonyloxy, e.g.

< RTI ID=8.2> ME thansulfonyloxy.< /RTI>

Preferably meant in a connection of the formula < RTI ID=8.3> IV< /RTI> the group of X the amino group of the formula VI, during in a connection of the formula V the remainder of Y mainly for a verätherte Mercaptogruppe, in particular Niederalkylthio, e.g. Methylthio, stands.

Salts of basic materials of the formulas IV and/or. V are < acidic addition salts; RTI ID=8.4> e.g. < /RTI> Salts with the above-mentioned acids, in particular with mineral acids, < RTI ID=8.5> wde< /RTI> Hydrogen halide-acidic, e.g. Hydrochloric acid, hydriodic acid or sulphuric acid. In particular of revision modification November heiress dung becomes the formula IV and/or. V different starting material and mainly a starting material of the formula V, where Y stands for a Mercaptogruppe verätherte if necessary or for a reactive, functional modified hydroxy group, in which uses form of an acidic addition salt.

The above reaction is accomplished in actually well-known way, e.g. in off or presence of a solvent or a solvent mixture, if desired, in presence of a surplus as starting material used of the amine component, under cooling or preferably under warming, e.g. at a temperature of approximately < RTI ID=8.6> 50 C< /RTI> until about < RTI ID=8.7> 180 " C, < /RTI> preferably with < RTI ID=8.8> 160 " C, < /RTI> if necessarily, in a closed vessel, if necessary under pressure, and/or under an inert gas, e.g. Nitrogen atmosphere;
The basic materials are well-known or can in actually well-known way be manufactured.

The new connections can be manufactured likewise, by one a connection of the formula
EMI9.1
where Y1 mean the Iminogruppe, a split offable group, which mean Oxo or Thioxogruppe, and Y2 a split offable group or Y1 and a Y2 collected a triple bound nitrogen atom, if R2 has the meaning of hydrogen, or the appropriate tautomere form, or a salt of it, with an alkyl diamine connection of the formula < RTI ID=9.1> H2N-Alk-NHR|< /RTI> (VIII) converts, and, if desired, accomplishes additional process steps.

A split offable group was defined already before under formula IV or V in connection with the substituents X or Y.

A bond of the formula VII becomes usually in the form of an acidic addition salt, in particular a salt with a mineral acid, like an hydrogen halide-acidic, e.g. Chlorine, bromine or hydriodic acid, assigned. The condensation to the ring can take place in or two stages.

The above reaction can being accomplished in off or presence of a solvent, like a preferably polar solvent. One works at ambient temperature or preferably at increased temperatures, e.g. with approximately < RTI ID=9.2> 50 " C< /RTI> until about < RTI ID=9.3> 20asc, < /RTI> whereby with absence of a solvent the mixture of the two reaction participants (the connection of the formula VII preferably in form of an acidic addition salt, and a connection of the formula VIII preferably in the surplus) on temperatures of approximately < RTI ID=9.4> 100 " C< /RTI> until about < RTI ID=9.5> 200au< /RTI> heated becomes. The reaction can in a closed vessel, if necessary under increased pressure, and/or under an inert gas, like nitrogen atmosphere, < RTI ID=9.6> vorgenommet< /RTI> become.

The basic materials are well-known or can in actually well-known way, for example those the formula VII, e.g. by treating an amine connection of the formula Py-NH-R2 < RTI ID=10.1> (IVa) < /RTI> with a suitable isocyanate or Isothiocyanat connection, like an ecyl isocyanate or - isothiocyanat, e.g. a Niederalkoxycarbonyl, < RTI ID=10.2> wïe< /RTI> Aethoxycarbonylisocyanat or - it isothiocyanat, or a Aroyl, like Benzoylisocyanat or - isothiocyanat (whereby these if necessary in situ, e.g. by treating an alkali metal or a Ammoniumcyanats or - thiocyanats with an appropriate Säurehalogenid, e.g. - chloride, or a suitable acidic ester, to be manufactured), removing the acyl group from received N-ecyl-urea or < RTI ID=10.3> N-.icyl-thiourea--< /RTI> connection by hydrolysis, preferably in presence of alkaline means, e.g. Sodium hydroxide, and converting the appropriate < RTI ID=10.4> Rarn < /RTI> material and/or. Thiourea intermediate product into the desired 0 and/or.

S-substituted ISO urea and/or. ISO thiourea connection of the formula VII by treating with a reactive ester of an alcohol, as < with one; RTI ID=10.5> Niederalkylhalogenid, < /RTI> e.g. Methyl chloride, - bromide or - iodid, or a Diniederalkylsulfat, e.g. Dimethyl sulfate, to be manufactured.

In a special procedure variant of the previous method one can likewise receive the new connections of the formula I, if one a connection of the formula
EMI10.1
where Z1 and Z2 stand together for oxygen or sulphur, and means Z3 the remainder of g 1 and Z4 hydrogen, or, Z2 and Z3 stands for Z1 for a split offable group together a connection forms, and Z4 the remainder of g 1 meant, ringschliesst, and, if desired, accomplishes additional process steps.

The Ringschluss of the above starting material of the formula IX can be accomplished by means of pyrolysis, whereby one < at temperatures from for instance 1000C to approximately; RTI ID=11.1> 200 " C, < /RTI> if necessarily or desired, in presence of a suitable high-boiling solvent, in a closed vessel, if necessary under increased pressure, and/or under an inert gas, e.g. Nitrogen atmosphere, works.

The starting material can be manufactured in actually well-known way, e.g. by treating a connection of the formula Py-N=C=Z (X) or the formula < RTI ID=11.2> Py-n (R2) - C (=Z) - Hall< /RTI> < RTI ID=11.3> (XI), < /RTI> where

resound for halogen, in particular to chlorine < RTI ID=11.4> and 1< /RTI> < RTI ID=11.5> For Sauerstoff< /RTI> or sulphur stands, with an alkyl diamine connection of the formula < RTI ID=11.6> H2N-Alk-NH-Rl< /RTI> < RTI ID=11.7> (VIII). < /RTI>

The new connections of the formula I can be received likewise, by < RTI ID=11.8> ein< /RTI> < RTI ID=11.9> Phosphinsäurehalogenid< /RTI> the formula
EMI11.1
where Hal halogen means, with an amine connection of the formula Py-NH-R2 < RTI ID=11.10> (IVa) < /RTI> converts, and, if desired, accomplishes additional process steps.

In a starting material of the formula XII Hal is mainly chlorine, and the reaction with the amine connection of the formula IVa becomes in absence, usually however in presence of a solvent, like a high-boiling solvent, e.g. Kylol, preferably at increased temperature, e.g. with approximately < RTI ID=11.11> lOO4C< /RTI> until about < RTI ID=11.12> 2004C, < /RTI> if necessarily, in a closed vessel, if necessary under increased pressure, or in an inert gas, e.g. Nitrogen atmosphere, accomplished.

< RTI ID=12.1> Ausgangsstoffe< /RTI> are well-known and can actually well-known wise in be manufactured. Thus one e.g. receives. Connections of the formula < RTI ID=12.2> SII, < /RTI> by one a connection of the formula
EMI12.1
with Phosphoroxychlorid, e.g. in presence of chloroform as solvents, at a temperature of approximately < RTI ID=12.3> 20 " C< /RTI> until about < RTI ID=12.4> 40 " C< /RTI> converts.

If desired, connections can be transferred of the formula I into other connections of the formula I. So one can e.g. in connections of the formula I, where g 1 and/or R2 hydrogen mean, these in actually well-known way, e.g. by treating the appropriate bond with a reactive ester of a Niederalkanols, like e.g. with a Niederalkylhalogenid. Methyl or ethyl chloride, - bromide or - iodid, or a the down alkyl sulfate, < RTI ID=12.5> e.g. < /RTI> Dimethyl sulfate, by Niederalkyl, e.g. Methyl or ethyl, replace.

One works in off or preferably in presence of a solvent, if necessarily, under cooling or warming, e.g.

in a temperature range of approximately < RTI ID=12.6> OOC< /RTI> to for instance 1000C, in a closed vessel, if necessary under increased pressure, and/or in an inert gas, e.g. Nitrogen atmosphere.

Furthermore connections of the formula I, in which the remainder is ?Py? by halogen, for example by chlorine or bromine, substituted, can be dehalogeniert. The Dehalogenierung can take place with reducing working materials, in particular with catalytic excited hydrogen or nascierendem hydrogen. The replacement of the halogen effected for example via hydrogen in presence of Raney nickel in < RTI ID=12.7> for example--alkoholischer< /RTI> Solution, in presence of platinum in ice vinegar or preferably in presence of palladium on carbon in aqueous solution with use salts of the too enthalogenisierenden connection or in solvents inert for the reaction.

As solvents for example ethers can, like e.g. Tetrahydrofuran or Dioxan, low alkane oils, as < RTI ID=13.1> e.g. < /RTI> Methanol or ethanol or also solvent mixtures, like e.g. < RTI ID=13.2>. Methanol/Formamid< /RTI> are used. The reaction is up to < for example at ambient temperature, can however also at easily increased temperature, for example at a temperature; RTI ID=13.3> 60oC< /RTI> and easy positive pressure to be implemented. The Enthalogenierung can be implemented however also with nascierendem hydrogen, for example with zinc, in particular with Zinkstaub or also metallic copper. Furthermore also sodium amalgam and Natriummethylat can or also - äthylat in alcoholic solution to be used.

Connections of the formula I, in which the remainder of ?Py? doubly by halogen, for example by chlorine or bromine in 2 - and 6-Stellung substituted are, can by conversion with a if necessary substituted amine to connections of the formula I be transferred, in which a halogen atom in 2-Stellung was replaced by a if necessary substituted Amino.

The conversions with a if necessary substituted amine are preferably implemented if necessary for example in alcoholic solution at erhähter temperature, return flow temperature of the reaction mixture and with positive pressure.

Connections of the formula I, in which the remainder < RTI ID=13.4> ?Py " < /RTI> doubly by halogen in 2 - and 6-Stellung substituted are, can of appropriate 2-Halogen-6-hydroxy or -6-niederalkoxyverbindungen by conversion with a Halogenierungsmittel, for example a chlorination means such as Phosphoroxychlorid be made.

Are in < RTI ID=13.5> RestPy " < /RTI> as substituent Niederalkoxygruppen, like e.g. Methoxy or Aethoxygruppen or also Phenoxygruppen available, then leave themselves easily by sour or basic hydrolysis in connection < these; RTI ID=13.6> Formula .1< /RTI> convert, in which the remainder is ?Py? by Hydroxy substituted. The new basic materials and methods to the making are likewise subject-matter of the invention,
Depending upon procedural conditions and basic materials one receives the connections of the formula I in free form or in form of their salts, which can be converted in usual way into one another or into other salts. Acidic addition salts e.g. leave themselves. receive by shifting of a free connection of the formula I with an acid, in particular to an organic or inorganic acid, which is suitable for the formation of pharmaceutical usable salts. As such acids are for example mentioned: Hydrogen halide-acidic, sulphuric acids, phosphoric acids, nitric acid, perchloric acid, aliphatic, alicyclische, aromatic or heterocyclic carbon or sulphonic acids, as ant, < RTI ID=14.1> Vinegar, < /RTI> Prop.-ion, amber, glycol, < RTI ID=14.2> Milk, < /RTI> Apple, wine, lemon, mark in, Hydroxymalein or Brenztraubensäure; Phenylessig, Benzoe, p-Aminobenzoe, Anthranil, < RTI ID=14.3> p-Hydroxy-< /RTI> benzoe, Salicyl or p-Aminosalicylsäure, Embonsäure, < RTI ID=14.4> Methane-sulfone, < /RTI> Ethane sulfone, Hydroxyäthansulfon, ethylen-sulfone-acidic; Halogen benzene sulfone, toluol sulfone, Naphthalinsulfonsäure or Sulfanilsäure; or ascorbic acid; Methionine, Trypthophan, lysine or arginin acid addition salts of bonds of the formula I can e.g. by treating with alkaline agents, like alkali metal hydroxides, or basic ion-exchangers into the free bases or e.g. by treating with suitable ion-exchangers or silver salts into other salts to be transferred.

The invention relates to also those embodiments of the method, after which one goes out with, on any stage of the method as intermediate product available junction and accomplishes the missing process steps, or which breaks methods off on any stage, or with which one a starting material on the reaction conditions or a reaction component

forms if necessary in form of a derivative, e.g. a salt, begins.

Received isomer mixtures can do that after actually well-known Metho, e.g. by fractional distillation, crystallization and/or
Chromatography, into which individual isomers are separated.

< RTI ID=15.1> Zweckmässig< /RTI> uses one for the lead-through of the methods according to invention those basic materials, which particularly lead to initially the particularly mentioned groups final materials emphasized described by final materials and to the particular or.

The present invention concerns besides the bonds of the formula I and of them pharmaceutical usable, non-toxic acidic addition salts to the use as medicaments, in particular as Antihypertensiva, e.g. to the treatment of increased blood pressure, as well as their use to the making of pharmaceutical, in particular antihypertensiv effective preparations.

The present invention concerns likewise pharmaceutical preparations, which connections of the formula I or pharmaceutical usable < RTI ID=15.2> Säureadditiaussalze< /RTI> contain from such connections. With the pharmaceutical preparations according to invention it acts around such for the enteralen, how oral rektalen or, as well as parenteral administration, which alone or together with a pharmaceutical applicable carrier material contains the pharmakologischen active substance.

The new pharmaceutical preparations contain from approximately 10% to approximately 95%, preferably from approximately 20% to approximately 90% the active substance.

Pharmaceutical preparations according to invention in dose unit forms e.g. are. Dragee, tablets, capsules, suppositories or ampoules.

The pharmaceutical preparations of the present invention become in actually well-known way, e.g. by means of conventional mixing, granulation, Dragier, solution or lyophilization procedure manufactured.

So one can receive pharmaceutical preparations to the oral application, by one the active substance with solid carrier materials and if necessary auxiliary materials combined, a received mixture if necessary granular, and the mixture and/or. Granular material, if desired or necessary, after addition of suitable auxiliary materials, to tablets or dragee cores processes.

Suitable carrier materials are in particular fillers, like sugar, e.g. Lactose, Saccharose, Mannit or Sorbit, cellulose preparations and/or calcium phosphates, e.g. Tri calcium phosphate or < RTI ID=16.1> Calciushydrogen < /RTI> phosphate, furthermore adhesive, like starch pastes, manufactured e.g.

using corn, wheat, rice or potato strength, gelatine, Traganth, methyl cellulose, Hydroxypropyl methylcellulose, Natriumcarboxymethylcellulose and/or polyvinylpyrrolidone, as well as if necessary explosive, like the above-mentioned starch, furthermore Carboxymethylstärke, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt of it, like Natriumalginat. Aids are mainly flow adjustment and lubricants, < RTI ID=16.2> zvB.< /RTI> Silicic acid, talc, stearic acid or salts of it, like magnesium or Calciumstearat, and/or PL glycol dragee cores are provided with suitable, if necessary gastric juice-resistant coatings, whereby one and others concentrated sugar solutions, which < RTI ID=16.3> gegebenenfälls< /RTI> Arab rubber, talc, polyvinylpyrrolidone, Polyäthylenglycol and/or titanium dioxide contain, lacquer solutions in suitable organic solvents or solvent mixtures or, to the preparation cellulose preparations suitable by gastric juice-resistant coatings, solutions of, how Acetylcellulosephthalat < or; RTI ID=16.4> Hydroxypropylmethylcellulose < /RTI> phthalat, uses. The tablets or dragee coatings can dyes or pigments, e.g. to the identifying or to the marking of different active substances, to be attached.

Further oral applicable pharmaceutical preparations are putting caps from gelatine, as well as soft, closed capsules from gelatine and a plasticiser, like Glycerin or Sorbitol. The putting caps know the active substance in form of a granulate, e.g. contain in the mixture with fillers, like lactose, adhesives, like starch, and/or lubricants, like talc or magnesium stearate, and if necessary of stabilisers. In soft < RTI ID=16.5> Rapseln< /RTI> the active substance preferably is in suitable fluids, as fat oils, paraffin oil or liquid PL glycols, solved or suspended, whereby stabilisers can be likewise caused.

As rektal applicable pharmaceutical preparations e.g. come.

Suppositories in consideration, which consist of a combination of the active substance with a Suppositoriengrundmasse. As Suppositoriengrundmasse are e.g. suitable. natural or synthetic Triglyceride, paraffin hydrocarbons, PL glycols or higher alkane oils.

Furthermore also gel Rektalkapseln can be used, be contained the one combination of the active substance with a basic dimension; as basic dimension.materials come < RTI ID=17.1> e.g. < /RTI> liquid Triglyceride, PL glycols or paraffin hydrocarbons in question.

For the parenteral administration mainly aqueous solutions of an active substance in water-soluble form are suitable, e.g. a water-soluble salt, furthermore suspensions of the active substance, like appropriate oily injection suspensions, whereby one greases suitable lipophilic solvents or vehicles, as oils, e.g. Sesamöl, or synthetic fatty acid esters, e.g. Ethyl oleate or Triglyceride, uses, or aqueous injection suspensions, which viscosity-increasing materials, e.g. sodium carboxymethylcellulose, Sorbit and/or dextran, and if necessary also of stabilisers contain.

The invention < RTI ID=17.2> umfasst< /RTI> likewise the use of the connections of the formula < RTI ID=17.3> I< /RTI> or of pharmaceutical usable non-toxic salts of such connections as pharmakologisch effective materials, in particular as Antihypertensiva, preferably in the form of pharmaceutical preparations. The dosage of the active substance depends on the Warmblüter species, the body weight and age and on the individual condition, as well as on the application way. By approximately 70 kg body weight a daily dose from approximately 25 to approximately 400 mg is preferably given to a Warmblüter on the average, from approximately 50 to approximately 200 mg active substance.

The following examples illustrate the invention described above; they are to limit however these to their extent in no

way. Temperatures are indicated in centigrades.

Example 1: A suspension of 37.4 g of the hydraulic iodide of n (2,6-Dimethyl-4-pyrimidinyl) - S-methyl-isothioharnstoff in 200 ml methanol is shifted with 7.6 g ethylen diamine and on the water bath heated. After 5 minutes one receives a clear solution, which is cooked during one hour under return flow. The solvent is < with the help of one; RTI ID=18.1> Rotationsverdampfers< /RTI> under decreased pressure far away and the residue during 2 hours with < RTI ID=18.2> 1500< /RTI> heated. After completion of the Methylmercaptan splitting off the mixture is cooled down, mixed into a paste with in Diäthyl ether and filtered then. The filter arrears become in 50 ml hot third. - Stand for Butanol suspended and some time calmly. < RTI ID=18.3> Män< /RTI> filtered, < so the hydraulic iodide washes with isopropanol after and keeps; RTI ID=18.4> 2-E (2,6-Dimethyl-4-pyrimidinyl) - amino] - 2< /RTI> imidazolins, F. < RTI ID=18.5> 269-2714.< /RTI>

The so available salt is loosened in 200 ml water, which filters solution off with 2-n of aqueous sodium hydroxide solution alkaline posed and the crystalline material. One loosens the free cousin in chloroform, who solution < over magnesium sulfate; RTI ID=18.6> getrocknet< /RTI> and evaporated. One keeps < as residue; RTI ID=18.7> 2 {(2,6-Dimethyl-4-pyrimidinyl) - < /RTI> < RTI ID=18.8> amino-2-imidazolin< /RTI> in the form of white crystals, F. < RTI ID=18.9> 229-230.< /RTI>

A further quantity of the product can be received by extracting the aqueous mother liquor with chloroform.

The hydrochloride of < RTI ID=18.10> 2 [(2, 6-Dimethyl-4-pyrimidinyl) - amino] - 2-< /RTI> imidazolin can be received, by treating a solution of the free connection in isopropanol with the computed quantity of a l.9-n solution of hydrogen chloride in ethanol. The crystalline product melts with < RTI ID=18.11> 298-300 ". < /RTI>

The starting material can be manufactured as follows: A suspension of 12.3 g 4-Amino-2,6-dimethyl-pyrimidin in 50 ml chloroform is < drop by drop with 13.1 g; RTI ID=18.12> Aethoxycarbonyl isothiocyanat< /RTI> treated, and the mixture during one hour under return flow heated. With the cooling crystallizes < RTI ID=18.13> N (2,6-Dimethyl-4-pyrimidinyl) - < /RTI> < RTI ID=18.14> N' äthoxycarbonyl thioharnstoff< /RTI> out and from 90%-igem aqueous ethanol one recrystallizes; it melts with < RTI ID=18.15> 163-165. < /RTI>

12,7 g of the so available < RTI ID=19.1> N (2,6-Dimethyl-4-pyrimidinyl) - N'-< /RTI> äthoxycarbonyl-thioharnstoffs wird mit 70 ml einer l-n wässrigen <RTI ID=19.2>Natriumhydroxid-Lösung</RTI> shifted, and the mixture during one hour cooked. With the cooling falls < RTI ID=19.3> N (2,6-Dimethyl-4-pyrimidinyl) - thio < /RTI> urea in the form of white crystals out, F. < RTI ID=19.4> 236-238 ". < /RTI>

A mixture of 20.4 g n (2,6-Dimethyl-4-pyrimidinyl) - thiourea and 130 ml methanol are treated with 16.7 g methyl iodide and cooked during one hour under return flow, whereby the starting material goes into solution. The solvent under decreased pressure one evaporates, and one receives the hydraulic iodide of the n (2,6-Dimethyl-4-pyrimidinyl) as residue - S-methyl-isothioharnstoffs in the form of white crystals, F. < RTI ID=19.5> 200-205 "; < /RTI> the product is processed without purification.

Example 2: A suspension of 35.7 g of the hydraulic iodide of n (2.6 Dimethoxy-4-pyrimidinyl) - S-methyl-isothioharnstoff in 750 ml methanol is shifted drop by drop with 12.0 g ethylen diamine in 100 ml methanol and cooked during 6 hours under return flow. After completion of the Methylmercaptan and ammonia development the reaction mixture under decreased pressure is restricted on a volume of approximately 100 ml and cooled during 16 hours. The crystalline precipitation is filtered off and washed with water, then with acetic acid ethyl ester; one keeps so < RTI ID=19.6> 2 - [(2, 6-Dimethoxy-4-pyrimidinyl) - amino] - 2-imidazo-< /RTI> lin, F. < RTI ID=19.7> 197-2004.< /RTI>

A suspension of 20 g < RTI ID=19.8> 2 {(2,6-Dimethoxy-4-pyrimidinyl) - amino] - < /RTI> 2-imidazolin and 200 ml ethanol are shifted with 39.6 ml a 2,26-n solution by hydrogen chloride in ethanol. The so available solution is restricted after the filtering under decreased pressure and shifted portionenweise with acetic acid ethyl ester, whereby crystallization begins. The crystalline material is filtered off and results in the hydrochloride < RTI ID=19.9> 2 [(2,6-Dimethoxy-4-pyrimidinyl) - amino] - 2-imida-< /RTI> zolins, F. < RTI ID=19.10> 193-195o.< /RTI>

The starting material can be received as follows: A mixture of 29.0 g < RTI ID=20.1> 4-Amino-2,6-dimethoxy-pyrimidin< /RTI> and 24,5 g < RTI ID=20.2> Aethoxycarbonyl isothiocyanat< /RTI> in 100 ml chloroform is cooked during 2 hours under return flow, cooled down then, and evaporated under decreased pressure, and that residue in 200 ml hot 95 per cent aqueous ethanol suspends. One cools, filters the precipitation off and washes with a mixture of ethanol and acetic acid ethyl esters down after. < RTI ID=20.3> N (2,6-Dimethoxy-4-pyrimitinyl) - N' äthoxyzarbonyl < /RTI> thiourea is received in the form of yellow crystals, F. < RTI ID=20.4> 177-180. < /RTI>

A mixture of 14.3 g < RTI ID=20.5> N (2,6-Dimethoxy-4-pyrimidinyl) - N'-< /RTI> äthoxycarbonyl thiourea and 90 ml LN an aqueous sodium hydroxide solution are cooked during 90 minutes under return flow, whereby the starting material goes first into solution and the crystalline product precipitates then. This is filtered off, washed with water and < in 100 ml a hot; RTI ID=20.6> 1: 1-Gemisches< /RTI> from isopropanol and petroleum ether suspends. < RTI ID=20.7> N (2, 6-Dimethoxy-4-pyrimidinyl) - thioharnstoff< /RTI> wird in Form von gelben Kristallen erhalten, F. < RTI ID=20.8> 237-238. < /RTI>

A suspension of 24.4 g < RTI ID=20.9> N (2,6-Dimethoxy-4-pyråmidinyl) - thio < /RTI> urea in 2500 ml acetone is treated drop by drop with 64.8 g methyl iodide and cooked under agitating during one hour under return flow. One receives a clear solution, which clouds itself briefly thereafter again after short time and a crystalline material separates. This is filtered off and results in the hydraulic iodide of the n (2,6-Dimethoxy-4 < RTI ID=20.10> pyrimidinyl) - S-methyl-isothioharnstoffs, < /RTI> F. < RTI ID=20.11> 185-187, < /RTI> without further purification one uses.

Example 3: 12.3 g < RTI ID=20.12> 4-Amino-2,6-dimethyl-pyrimidin< /RTI> and 18.3 g of the hydraulic iodide of < RTI ID=20.13> 2-Methylthio-2-imidazolin< /RTI> and if well through-mixed is pulverized, then on a bath temperature of < RTI ID=20.14> 190 < /RTI> heated, with which temperature < RTI ID=20.15> Methylmercaptanabspaltung< /RTI> begins. The bath temperature is lowered on 1700; one leaves during 1 hour at this temperature, cools then on < RTI ID=20.16> 50 < /RTI> and the warm melt solves in one < RTI ID=20.17> 1: 1-Gemisch< /RTI> of acetone and methanol. One filters and steams that Filtrate under decreased pressure to dry ones in. The residue is taken and filtered

in a mixture by isopropanol and acetone on; the residue represents the hydraulic iodide to 2 [(2,6-Dimethyl-4-pyrimidinyl) amino] - 2-imidazolins and between 2-n of aqueous sodium hydroxide solution and dichloromethane is distributed. The organic phase is separated, dried and evaporated over magnesium sulfate.

One receives as halfcrystalline residue 2 [(2,6-Dimethyl-4-pyrimidinyl) - amino] - 2-imidazolin, which is taken in water on and filtered off in crystalline form, F. < RTI ID=21.1> 225-2290.< /RTI> The product shows no mixing melting point depression with a sample after the method of the example of 1 available material and is < according to Dünnschichtchroma; RTI ID=21.2> togrnmm< /RTI> (System: Methanol) identically to this.

A further quantity of the free connection can from the Isopropa < RTI ID=21.3> NO VAceton Mutterlauge< /RTI> are received, by under decreased pressure evaporating these, the residue in water solves, the aqueous solution with 2-n. alkaline to aqueous sodium hydroxide solution places and with dichloromethane extracted. The organic excerpt is solved evaporated, the residue in water, and the solution with a small quantity of 2-n. for aqueous sodium hydroxide solution shifts and cooled. The crystalline precipitation is filtered off; it melts with < RTI ID=21.4> 227-229. < /RTI>

Example 4: A solution of 11 g of the hydraulic iodide of n (4,6-Di < RTI ID=21.5> methoxy-2-methyl-5-pyrimidinyl) - S-methyl-isothiOharnstoff< /RTI> and 2.1 g ethylen diamine in 100 ml during 10 hours under return flow one cooks for absolute ethanol. Subsequently, one evaporates under decreased pressure, mixes the residue well with a satisfied aqueous sodium carbonate solution and filters the precipitation off. After recrystallizing from dimethyl formamides one receives 2 [(4,6-Dimethoxy < RTI ID=21.6> 2-methyl-5-pyrimidinyl) - amino] - 2-imidazolin, < /RTI> F. < RTI ID=21.7> 2294.< /RTI>

The starting material is manufactured as follows: A solution of 4,2 g ammonium thiocyanat in 25 ml acetone with 6 ml Benzoylchlorid is shifted; the mixture is boiled up briefly and treated then drop by drop with a solution by 8,5 g 5-Amino-4,6-dimethoxy-2methyl-pyrimidin in 45 ml acetone. Subsequently, one still cooks during 15 minutes under return flow and pours then the reaction solution in < RTI ID=22.1> 500< /RTI> ml water. The failed product is filtered off and washed well with water, taken up then in a hot solution by 8 g sodium hydroxide to 80 ml water. One cooks during 5 minutes under return flow, cools and sets the pH value by addition of 2-n.Salzsäure to 9, on which < RTI ID=22.2> N (4,6-Dimethoxy-2-methyl-5-pyrimidi-< /RTI> nyl) - thiourea crystallizes, which < after recrystallizing from a mixture from water and Dioxan with; RTI ID=22.3> 214-215< /RTI> melts.

A mixture of 8,9 g n (4,6-Dimethoxy-2-methyl-5-pyrimidinyl) thiourea and 8.5 g methyl iodide in 800 ml methanol is cooked during 3 hours under return flow and restricted under decreased pressure strongly. The hydraulic iodide < RTI ID=22.4> N (4,6-Dimethoxy-2-methyl-5-pyrimidinyl) - < /RTI> S-methyl-isothioharnstoffs thereby, F crystallizes. < RTI ID=22.5> 168-170, < /RTI> and without purification one processes.

Example 5: A mixture of 40,0 g of the hydraulic iodide of n (2,6-Di < RTI ID=22.6> methyl-4-pyrimidinyl) - S-methyl-isothioharnstoff< /RTI> and 18.3 g propylene diamine in 200 ml during 6 hours under return flow are cooked for methanol. One cools down, filtered and evaporates the clear solution under decreased pressure to dry ones. The residue is taken in 100 ml water on and extracted three times with ever 150 ml chloroform. The organic excerpt is dried and evaporated over magnesium sulfate.

One keeps so < RTI ID=22.7> 2 [(2, 6-Dimethyl-4-pyrimidinyl) - aminc - l, 4,5,6-< /RTI> tetrahydro pyrimidin, F. < RTI ID=22.8> 161-163, < /RTI> into the hydrochloride one transfers as follows:
One in the warmth prepared solution of 12 g 2 [(2,6-Dimethyl < RTI ID=22.9> 4-pyrimidinyl) - amino] -1.4.5, 6-tetrahydropyrimidin< /RTI> in 80 ml isopropanol is shifted with 42,7 ml a 2,7-n solution by hydrogen chloride in ethanol. The solution is restricted under decreased pressure on for instance a third of the volume and diluted portionenweise with acetic acid ethyl ester. The crystalline precipitation is filtered off and it gives the Dihydrochlorid 2 [(2,6-Dimethyl-4-pyrimidinvl) - aminol < RTI ID=23.1> 1,4,5,6-tetrahydro-pyrimidins, < /RTI> F. < RTI ID=23.2> 255-258. < /RTI>

Example 6: Zu einer Lösung von 7,2 g Aethylendiamin in 30 ml Methanol tropft man eine Lösung von 20,6 g N-(6-Chlor-2-methyl-4-pyrimidinyl)-S-methyl-isothioharnstoff-hydrojodid in 300 ml Methanol. The interior temperature amounts to 650 and during 6 hours is maintained. After terminated development of Methylmercaptan and ammonia at the rotary evaporator and the residue in 150 is evaporated is suspended, sucked off ml water and washed with water. The raw cousin melts with < RTI ID=23.3> 207-209 ". < /RTI>

The hydrochloride is received, by shifting 16.6 g of the raw cousin in 200 ml hot ethanol suspended and with 34,1 ml 2,3-n äthanolischer hydrochloric acid, which filters received clear solution with activated charcoal, to approx. and with ethyl acetate and little ether the hydrochloride evaporates 80 ml at the rotary evaporator < RTI ID=23.4> 2-t (6-Chlor-2-< /RTI> < RTI ID=23.5> methyl-4-pyrimidinyl) - amino] - 2-imidazolins zur< /RTI> Crystallization brings, F. < RTI ID=23.6> 299-301 < /RTI> (Zers.).

< RTI ID=23.7> as< /RTI> Basic material serving isothiourea is received as follows: a) 65.2 g < RTI ID=23.8> 4,6-Dichlor-2-methyl-pyrimidin< /RTI> in 750 ml ethanol with 100 g liquid ammonia in autoclaves 12 hours with are < RTI ID=23.9> 804< /RTI> agitated, that separated ammonium chloride is evaporated filtered off, at the rotary evaporator, the residue in 1 litre water is hot suspended and sucked off. From the aqueous mother liquor become by vaporizing on approx. 100 ml further quantities of the 4-Amino-6chlor-2-methyl-pyrimidins won. The united raw products are umgelöst, < from ethyl acetate; RTI ID=23.10> F. 185-187'.< /RTI>

b) solved 28.7 g of the cleaned product in 200 ml chloroform and 50 ml dimethyl formamides will become, the solution 26.2 g Aethoxycarbonyl isothiocyanat admitted and the mixture 2 hours on < RTI ID=23.11> 80< /RTI> warmed up. One cools, evaporated and crystallizes the residue, which < RTI ID=23.12>
1 3 N -(6-Chlor-2-methyl-4-pyrimidinyl) -N -äthowyzarbonyl-thioharnstoff</RTI> from ethanol over, F. < RTI ID=24.1> 142-143. < /RTI>

c) By saponification with LN. Sodium hydroxide solution (1 hour < RTI ID=24.2> 130) < /RTI> becomes the n (6-Chlor-2-methyl-4-pyrimidinyl) - thiourea of the F. < RTI ID=24.3> 230 < /RTI> (Discoloration and sinters) receive.

d) 13.5 g of this thiourea in 1500 ml acetone are suspended, with 37,8 g methyl iodide shifted and 2 hours under return

flow cooked.

After 15 minutes solution occurs. The solvent is evaporated at the rotary evaporator, the crystals staying in ethers and insulated, F are suspended. < RTI ID=24.4> 179C< /RTI> (Zers.). It concerns as starting material the specified Isothioharnstoff hydroj odid.

Example 7: 10.6 g after example 6 of the received < RTI ID=24.5> 2 [(6-Chlor-2-< /RTI> < RTI ID=24.6> methyl-4-pyrimidinyl) - amino] - 2-imidazolin-Base< /RTI> become in 200 ml water and 50 ml LN. Salzsäure gelöst, mit 1 g 10%-igem Palladium-auf-Kohle versetzt und unter leichtem (0,2 bar) Ueberdruck mit Wasserstoff bei <RTI ID=24.7>48"</RTI> vibrated. After admission of the computed quantity (1120 ml), evaporated at the rotary evaporator and recrystallized the crystalline residue in ethanol methanol 1:1 is interrupted, filtered hot.

The received crystals 2 [(2-Methyl-4-pyrimidinyl) - amino] - 2-imidazolin-dihydrochlorids melt with < RTI ID=24.8> 252-255. < /RTI>

Example 8: 24.0 g < RTI ID=24.9> & (6-Chlor-2-methoxy-4-pyrimidinyl) - S-methyl-< /RTI> ISO thiourea hydraulic iodide are solved in 300 ml methanol and course-dripped to 8.0 g ethylen diamine in 75 ml methanol. One heated 6 hours under agitating at return flow temperature, whereby crystallization occurs, restricts water at the rotary evaporator and suspends the residue in 200 ml. Subsequently, insulated is washed and with water.

One keeps so < RTI ID=24.10> 2 [(6-Chlor-2methoxy-4-pyrimidinyl) - amino] - 2-imida-< /RTI> zolin of the melting point < RTI ID=24.11> 216-219. < /RTI>

Hydrochloride: 11.5 g cousin are suspended in 50 ml methanol, and admitted 1 equivalent 2,4-n äthanolischer hydrochloric acid. Man verdünnt mit 50 ml Aethanol, filtriert mit Celite und <RTI ID=24.12>verdampftdieklareMutter-</RTI> caustic solution at the rotary evaporator on half. After addition of 100 ml acetone falls the hydrochloride < RTI ID=25.1> 2 [(6-Chlor-2-methoxy-4-pyrimidinyl) < /RTI> amino]-2-imidazolins vom F. < RTI ID=25.2> 220 < /RTI> crystalline out.

The isothiourea used as starting material is won analog for the example 6: a) From 63,8 g < RTI ID=25.3> 4-Amino-6-chlor-2-methoxy-pyrimidin< /RTI> (made of 2,6-Dichlor-4-amino-pyrimidin and Natriummethanolat in methanol with 800 outside temperature) and 52.4 g Aethoxycarbonyl isothiocyanat in simmering acetone one < RTI ID=25.4> N (6-Chlor-2-methoxy-4-pyrimidinyl) - N - < /RTI> < RTI ID=25.5> äthoxycarbonyl thioharnstoff< /RTI> of the F. < RTI ID=25.6> 160-164 > < /RTI> received.

b) The saponification of this ester with 150 ml LN sodium hydroxide solution in the simmering heat results in a crystalline precipitation. Solution and precipitation are weakly more acidic placed with 10 ml glacial acetic acid, whereby under foaming the Decarboxylierung occurs. One the insulated n (6-Chlor < RTI ID=25.7> 2-methoxy-4-pyrimidinyl) - thiourea, < /RTI> F. over < RTI ID=25.8> 330< /RTI> and washes it with water.

c) In such a way received urea becomes as in example 6 with methyl iodide into the ISO thiourea hydraulic iodide of the F, specified as starting material. 1670 (Zers.) transferred.

Example 9: 11.5 g after example 8 received 2 [(6-Chlor-2 < RTI ID=25.9> methoxy-4-pyrimidinyl) - amino]--2-imidazolins< /RTI> in 200 ml methanol and 100 ml dimethyl formamides (purissimum) are suspended and 2 g are < RTI ID=25.10> 10%-iger< /RTI> Palladium carburizing catalyst admitted and at 0,2 bar positive pressure and a temperature of < RTI ID=25.11> 49 < /RTI> with hydrogen treats. The absorption of hydrogen runs more slowly than in example 7. After its completion the catalyst is evaporated filtered, the mother liquor at the rotary evaporator, the residue with 100 ml LN sodium hydroxide solution and taken off with chloroform is shifted. < RTI ID=25.12> Chloroform Rückstand< /RTI> consists of a slowly crystallizing cousin, that is transferred directly into its hydrochloride, by shifting acetone with 1 equivalent äthanolischer hydrochloric acid in 50 ml, then by addition of acetone and Ethyl acetate is crystalline separated. The received < RTI ID=26.1> 2-t (2-Methoxy-4-< /RTI> < RTI ID=26.2> pyrimidinyl) - amino] - 2-imitazolin-hydrochlorid< /RTI> melts with < RTI ID=26.3> 170-172 < /RTI> (Zers.).

Example < RTI ID=26.4> IO: < /RTI> 22.75 g after example 8 received 2 [(6-Chlor-2methoxy-4-pyrimidinyl) - amino] - imidazolins in 100 ml LN of aqueous hydrochloric acid and 300 ml water are solved, with 2 g 10%-iger palladium-carburize shifted and at 0,2 bar positive pressure and < RTI ID=26.5> 60 < /RTI> Interior temperature hydrogenates. After admission of 2320 ml (more ber. 2240 ml) one interrupts, one abgenutscht by the catalyst and one evaporates at the rotary evaporator completely. The residue is evaporated twice with 100 ml alcohol, the crystals in 150 ml isopropanol and renewed-insulated are hot suspended. Due to cracking of the Methoxygruppe is < RTI ID=26.6> 2 {(2-< /RTI> < RTI ID=26.7> Hydroxy-4-pyrimidinyl) - amino -2-imidazolin-hydrochlorid< /RTI> developed and points an F. of < RTI ID=26.8> 256-258a< /RTI> (Zers.) up.

Example 11: 28.0 g < RTI ID=26.9> N (6-Chlor-2-dimethylamino-4-pyrimidinyll-S-< /RTI> methyl ISO thiourea hydraulic iodide are solved in 400 ml methanol and < to a solution from 9,0; RTI ID=26.10> g< /RTI> Ethylen diamine in 75 ml methanol course-drips. One agitates 6 hours at return flow temperature, whereby ammonia and Methylmercaptan development are stopped and are separated crystals. One confines the suspension in < RTI ID=26.11> dampfer< /RTI> on approx. ml, the crystalline portion with 150 ml water sucks, mixes 75 off, insulated it and washes with water and isopropanol.

The received < RTI ID=26.12> 2C (6-Chlor-2-dimethylnmino-4-pyrimidinyl) - amino] - 2-< /RTI> imidazolin melts with < RTI ID=26.13> 268-271 ". < /RTI> After recrystallization from Dimethylsulfoxid methanol the product melts with < RTI ID=26.14> 278-279. < /RTI>

The received cousin is < with the computed quantities; RTI ID=26.15> 2-n wässriaer< /RTI> Hydrochloric acid shifts, whereby the hydrochloride partly crystallizes.

By addition of of the quadruple quantity water with 750 a clear is received solution, the which after filtration at rotary evaporator evaporated, which suspends residue in isopropanol, one sucks off and one washes with ethyl acetate. The hydrochloride melts with < RTI ID=26.16> 279-2800.< /RTI>

To a suspension of 7,8 g cousin in 300 ml at ambient temperature 3.42 g methane-sulfone-acidic are admitted to water, whereby a clear solution develops. One evaporates that to the dry one and crystallizes Residue from methanol Aether over. In such a way received Methansulfonat melts with < RTI ID=27.1> 256-259. < /RTI>

The isothiourea used as starting material is won analog for example 6: a) From 4-Amino-2,6-dichlor-pyrimidin the 4-Amino-6-chlor-2-dimethylamino-pyrimidin of the F becomes with dimethylamine in methanol in exothermic reaction. < RTI ID=27.2> 151-152 < /RTI> manufactured. 34.5 g of this connection are < with 26,2 g; RTI ID=27.3> Aethoxycarbonyl isothiocyanat< /RTI> in 150 ml acetone under return flow converted to the N - (6-Chlor-2-dimethylamino-4-pyrimidinyl) < RTI ID=27.4> N3-äthoxycarbonyi-thicharnstoff< /RTI> of the F. < RTI ID=27.5> 206-208 ". < /RTI>

b) The saponification of this connection with 170 ml 1 n sodium hydroxide solution at return flow temperature supplies a thick crystal mash, which is sucked off and washed with water thoroughly. The received n (6-Chlor-2dimethylamino-4-pyrimidinyl) - thiourea melts with < RTI ID=27.6> 235 < /RTI> (Zers.).

c) 29.0 g of this thiourea are suspended into 2,9 litres acetone and shifted with 71 g methyl iodide. With heating up under return flow the suspension goes into solution and crystallizes briefly thereafter.

One cools and the insulated crystalline precipitation down of the n (6-Chlor-2 < RTI ID=27.7> dimethylamino4pyrimidiny1) - S-methyl-isothioharnstoff-hydrojodids< /RTI> of the F. 2204 (Zers.).

Example 12: 11.1 g < RTI ID=27.8> 2 [(6-Chlor-2-dimethylamino-4-pyrimidinyl) - < /RTI> < RTI ID=27.9> aminoj-2-imidazolin-Base< /RTI> (manufactured after example 11) LN become with 19,5 ml. Hydrochloric acid and 80 ml water solved, with 2 g 10%-igem palladium-carburize at 0,2 bar positive pressure at the hydrogen hydrogenated.

The temperature amounts to < RTI ID=27.10> 52-55. < /RTI> After 15 hours the computed quantity hydrogen (438 ml) is taken up. One filtered of the catalyst, restricts the aqueous mother liquor at the rotary evaporator, solves the residue in 75 ml isopropanol and lets crystallize. Erhal < RTI ID=27.11> tene 2 [(2-Dimethylamino-4-pyrimidinyl) - amino -2-imidazolin-dihydro-< /RTI> chloride melts with < RTI ID=27.12> 275-278< /RTI> (Zers.).

Example 13: In the same way as described in example 11, out one < RTI ID=28.1> 11,5< /RTI> g ethylen diamine in 100 ml methanol, to which 38.0 g < RTI ID=28.2> N (6-Chlor-2-diäthylamino-4-pyrimidinyl) - S-methyl-isothioharnstoff - < /RTI> hydrojodid in 200 ml Methanol zugetropft werden, nach 6 Stunden Rühren unter Rückfluss die <RTI ID=28.3>2-[(6-Chlor-2-diäthylamino-4-pyrimidinyl)-amino]-2-</RTI> Imidazolin cousin of the F. < RTI ID=28.4> 231-232 < /RTI> received. By suspending 21,5 g of the cousin in 50 ml methanol and addition of 2 equivalents (67 ml) ml ethyl acetates, the Dihydrochlorid is received to 2,39-n äthanolischer hydrochloric acid, followed of 300, which with drying in the high vacuum into the mono hydrochloride of the F. 203-205 ignores.

The starting material for the synthesis described above can be received in analogy to example 11: a) out < RTI ID=28.5> 4-Amino-2,6-dichlor-pyrimidin< /RTI> with < RTI ID=28.6> Diäthylaminüberschuss< /RTI> in methanol with < RTI ID=28.7> 80< /RTI> Aussentemperatur das 4-Amino-6-chlor-2-diäthylaminopyrimidin vom F. < RTI ID=28.8> 110, < /RTI> which as raw product is re-used; b) by conversion of 43,6 g of this pyrimidine with 28,5 g Aethoxycarbonyl isothiocyanat in simmering acetone < RTI ID=28.9> N1 (6-Chlor-2-diäthyl-< /RTI> amino-4-pyrimidinyl) - N < RTI ID=28.10> - N3-äthoxycarbonyl-thioharnstoff< /RTI> of the F. < RTI ID=28.11> 141-145; < /RTI> c) by saponification of the ester with 250 ml LN sodium hydroxide solution under return flow, received from 48,0 g, < RTI ID=28.12> N (6-Chlor-2-diäthylnmino-4-pyrimidi-< /RTI> nyl) - thiourea of the F. < RTI ID=28.13> 175-180; < /RTI> and D) from this raw thiourea (35.8 g) with 40 g methyl iodide in 750 ml acetone under return flow the n (6-Chlor-2-diäthylamino-4-pyrimidinyl), used as output product - S-methyl-isothioharnstoff < RTI ID=28.14> hydrojodid< /RTI> of the F. <RTI ID=28.15>178-180 </RTI> (Zers.).

Example 14: In gleicher Weise wie in den Beispielen 11 und 13 beschrieben, werden aus <RTI ID=28.16>N- (6-Chlor-2-di-n-butylamino-4-pyrimidinyl)-</RTI> < RTI ID=28.17> S-methyl-isothioharnstoff-hydrojodid< /RTI> and ethylen diamine in methanol < RTI ID=28.18> 2C (6-Chlor-2-di-n-butylamino-4-pyrimidinyl) - amino] - 2-imidazolin< /RTI> and its hydrochloride receive. The free cousin melts with < RTI ID=28.19> 167-168, < /RTI> the hydrochloride with < RTI ID=28.20> 148-150. < /RTI>

The starting material for this Dibutylaminoderivat is < in same reaction sequence as in the examples 11 and 13 from 4-Amino; RTI ID=29.1> 2-di-n-butylamino-6-chlorpyrimidin< /RTI> received.

Example 15: 10,3 g Aethylendiamin werden in 40 ml Methanol vorgelegt und unter Rühren bei <RTI ID=29.2>70a</RTI> 30.3 g n (6-Dimethylamino-2-methyl < RTI ID=29.3> 4-pyrimidinyl) - S-methyl-isothioharnstoff-hydrojOdid< /RTI> in 350 ml < RTI ID=29.4> Metha < /RTI> nol and the reaction mixture course-drips 6 hours at this temperature held. Das Lösungsmittel mit den suspendierten Kristallen wird im Rotationsverdampfer zur Trockne gebracht und der Rückstand in 300 ml Wasser suspendiert. A sample shows that the crystals contain still small quantities hydraulic iodide. They are solved therefore in 200 ml 2-n hydrochloric acid and with 5-n sodium hydroxide solution please. The crystalline cousin is washed insulated, twice with warm water, treated then with isopropanol and ether. One receives in such a way analysis-pure 2 [(6-Dimethylamino-2-methyl-4-pyrimidinyl) - amino] - 2-imidazolin, F. < RTI ID=29.5> 286-288. < /RTI>

Its hydrochloride is more äthanolischer < received, as the cousin in isopropanol suspends, with 1 equivalent; RTI ID=29.6> 2. , 3-n< /RTI> Hydrochloric acid transferred and with ethyl acetate as < RTI ID=29.7> Monohydrochlorid< /RTI> becomes, F pleases. < RTI ID=29.8> 281-283.< /RTI>

The starting material for the synthesis described above can be received to analog for the examples 11 and 13: a) from in example 6 used < RTI ID=29.9> 4-Amino-6-chlor-2-methyl-pyrimi-< /RTI> din vom Schmelzpunkt <RTI ID=29.10>185-187 </RTI> and the 4fachen theoretical quantity dimethylamine in methanol with < RTI ID=29.11> 120a< /RTI> im Druckgefäss das 4-Amino-6-di <RTI ID=29.12>methylamino-2-methylpyrimidin</RTI> of the F. < RTI ID=29.13> 176-179; < /RTI> b) by conversion of 29,0 g of this pyrimidine with 25,0 g Aethoxycarbonyl isothiocyanat in simmering chloroform < RTI ID=29.14> N (6-Dimethyl-< /RTI> <RTI ID=29.15>amino-2-methyl-4-pyrimidinyl)-N -

äthoxycarbonyl-thioharnstoff</RTI> of the F. < RTI ID=29.16> 140-143 < /RTI> (after recrystallizing from alcohol); c) durch Verseifen von 31,0 g des erhaltenen Esters mit 200 ml l-n Natronlauge bei Siedetemperatur der N-(6-Dimethylamino-2-methyl-4pyrimidinyl)-thioharnstoff vom F. < RTI ID=29.17> 245-247; < /RTI> and D) from 19,3 g of this received thiourea with 51,9 g methyl iodide in 2000 ml acetone and 200 ml methanol under return flow < RTI ID=30.1> N (6-Di-< /RTI> < RTI ID=30.2> methylamino-2-methyl-4-pyrimidinyl) -S-methyl-isothioharnstoff-hydro-</RTI> iodide of the F. < RTI ID=30.3> 225-227. < /RTI>

Example 16: Zu einer siedenden Lösung von 9,5 g Aethylendiamin in 50 ml Methanol werden 26,0 g N-(2,6-Dihydroxy-5-pyrimidinyl)-S-methylisothioharnstoff-hydrojodid in 500 ml warmem Methanol zugetropft und 15 Stunden unter Rückfluss gekocht. After short time a white precipitation begins to fail. One cools, sucks off and does not treat the precipitation, which contains heavysoluble hydraulic iodide beside the Imidazolin cousin, together with not converted ISO thiourea hydraulic iodide, several times 12 hours long with 500 for warm water, to which 10% methanol were added. The melting point rises thereby from 2680 (Zers.) to 2900 (Zers.) and remains finally with < RTI ID=30.4> 328-330 " < /RTI> constant. The latter melting point corresponds to the pure < RTI ID=30.5> 2-f (2,6-Di-< /RTI> hydroxy-5-pyrimidinyl)-amino]-2-imidazolin, das zum grössten Teil in seiner tautomeren Form, dem <RTI ID=30.6>2-[(2,6-Dioxo-1,2,3,6-tetrahydro-;-pyrimi-</RTI> dinyl) - amino] - 2-imidazolin is present.

The hydrochloride is received by releasing from 7,5 g of the cousin in 38,5 ml LN hydrochloric acid in the warmth. The solution is evaporated filtered, at the rotary evaporator, which occurs residue with 100 ml ethanol evaporated, to the residue of 50 ml ethyl acetates and 50 ml isopropanol admitted and agitated to crystallization. F. < RTI ID=30.7> 275 < /RTI> < RTI ID=30.8> (Zers.) < /RTI> < RTI ID=30.9> tristallwasserhaltige< /RTI> Hydrochlorides (F. < RTI ID=30.10> 1300< /RTI> Zers.) are < in; RTI ID=30.11> high < /RTI> vacuum dried to the melting point of < RTI ID=30.12> 275 < /RTI> is reached.

Das Ausgangsmaterial für die oben beschriebene Synthese wird in Analogie zu den Beispielen 11, 13 und 15 auf folgende Weise erhalten: a) 12.5 g 5-Aminouracil are suspended in 150 ml Dimethylsulfoxid and < 13.1 g; RTI ID=30.13> Aethoxycarbonyl isothiocyanat< /RTI> zugegeben. One agitates 3 hours with < RTI ID=30.14> 60, < /RTI> if a clear solution receives, this pours in water, sucks off and keeps < RTI ID=30.15> N (2,6-Dihydroxy-5-pyrimidinyl) - N - äthoxycarbonyl < /RTI> thioharnstoff, der zur Reinigung in siedendem Aceton suspendiert wird.

F. > <RTI ID=30.16>3000;</RTI> b) by in-hour saponification of this connection (12.9 g) with 150 ml LN sodium hydroxide solution at return flow temperature, cooling, shifting with totally 50 ml glacial acetic acid the crystalline is < RTI ID=31.1> N (2,6-Dihydroxy-5-pyrimidinyl) - < /RTI> thiourea of < RTI ID=31.2> F. $ 300 </RTI> erhalten, der zur Reinigung in heissem Isopropanol suspendiert wird; c) by shifting of 27,9 g of this connection with 21,3 g methyl iodide in 1800 ml methanol and 1000 ml dimethyl formamides with < RTI ID=31.3> 80 " < /RTI> wird das <RTI ID=31.4> N-(2,6-Dihydroxy-5-pyrimidinyl)-S-methyl-isothisharnstoff-hydrojOdid</RTI> vom F. <RTI ID=31.5>245 </RTI> (Zers.) erhalten.

Beispiel 17: Zu einer Lösung von 8,5 g Aethylendiamin in 80 ml Methanol wird die Lösung von 26,0 g N-(2,6-Diäthyl-5-methyl-4 <RTI ID=31.6>pyrimidinyl)-S-methyl-isothioharnstoff-hydrojOdit</RTI> in 250 ml Methanol zugetropft. Man kocht 12 Stunden unter Rühren, verdampft am Rotationsverdampfer zur Trockne, löst in Methylenchlorid, wäscht zweimal mit Wasser, verdampft das Lösungsmittel erneut, suspendiert den kristallinen Rückstand in Aethanol und erhält weisse Kristalle der Base vom F. < RTI ID=31.7> 128-1310, < /RTI> into the hydrochloride < RTI ID=31.8> 2 ((2,6-Diäthyl-5-methyl-< /RTI> <RTI ID=31.9>4-pyrimidinyl)-amino)-2-imidazolins</RTI> übergeführt werden, indem man 13,8 g der Base in Aethanol löst, 32,0 ml <RTI ID=31.10>l,82-n</RTI> äthanolische hydrochloric acid admits and < RTI ID=31.11> Hydrochlorid< /RTI> mit etwas Aether zur Kristallisation bringt. F. < RTI ID=31.12> 190-192 ". < /RTI>

Das Ausgangsmaterial für die oben beschriebene Synthese lässt sich analog zu den Beispielen 11, 13, 15 und 16 wie folgt erhalten: a) Aus 33,0 g <RTI ID=31.13>4-Amino-2,6-diäthyl-5-methyl-pyrimidin</RTI> <RTI ID=31.14> (Kyanäthin")</RTI> in 200 ml acetone and 50 ml dimethyl formamides and 26.2 g Aethoxycarbonyl isothiocyanat after 3 hours are < RTI ID=31.15> Rücfluss< /RTI> the N1 (2,6-Diäthyl < RTI ID=31.16> 5-methyl-4-pyrimidinyl) - N - athoxycarbonyl thioharnstoff< /RTI> vom F. <RTI ID=31.17>86-89 </RTI> received.

b) Aus 49,5 g dieser Verbindung durch Verseifen mit 100 ml 2-n Natronlauge unter Rückfluss, Neutralisieren mit Eisessig auf pH <RTI ID=31.18>i</RTI> one < RTI ID=31.19> N (2,6-Diäthyl-5-methyl-4-pyrimidinyl) - thioharnstoff< /RTI> of the F. <RTI ID=31.20>151-154 </RTI> erhalten.

c) Aus 17,1 g dieser Verbindung und 43,2 g Methyljodid in 400 ml heissem Aceton erhält man das N-(2,6-Diäthyl-5-methyl-4-pyrimidinyl)-S <RTI ID=32.1>methyl-isothioharnstoff-hydrojodid,</RTI> F. < RTI ID=32.2> 180-1820.< /RTI>

Beispiel 18: 27,0 g <RTI ID=32.3>N-(2-Phenyl-4-pyrimidinyl)-S-methyl-isot</RTI> urea hydraulic iodide in 300 ml methanol are course-dripped to 9.0 g ethylen diamine in 100 ml methanol. Man erwärmt 6 Stunden unter Rühren auf <RTI ID=32.4>80 ,</RTI> verdampft am Rotationsverdampfer zur Trockne, suspendiert die kristalline Verbindung in Wasser, dann in <RTI ID=32.5>Isopropanol-Aethergemisch</RTI> and insulated < in such a way; RTI ID=32.6> 2 [(2-Phenyl-4-pyrimidinyl) - amino] - 2-imidazolin< /RTI> vom F. <RTI ID=32.7>230-232 .</RTI>

Aus 15 g der Imidazolin-Base wird das Dihydrochlorid durch Suspendieren in Methanol (50 ml), Zugabe von 2 Aequivalenten 2,3-n äthanolischer Salzsäure (54,4 ml), Filtrieren der entstandenen Lösung und Zugabe von Essigester als Kristalle vom F. < RTI ID=32.8> 255-257 < /RTI> received.

Das oben verwendete Ausgangsmaterial wird über folgende Stufen erhalten: a) aus 51,3 g 4-Amino-2-phenyl-pyrimidin und 40 g <RTI ID=32.9>Aethoxycarbonyl-</RTI> isothiocyanat in 400 ml simmering acetone of the n (2-Phenyl-4-pyrimidi < RTI ID=32.10>
3..

nyl)-N -äthoxyzarbonyl-thioharnstoff vom F. 185-1880;</RTI> b) from 66,4 g of the ester by soaps with 300 ml LN sodium hydroxide solution in the simmering heat the n (2-Phenyl-4-pyrimidinyl) - thiourea of the F. 2370 (Zers.); c) aus 38,3 g dieses Thioharnstoffes und 100 g Methyljodid in 3, 8 Liter siedendem Aceton das <RTI ID=32.11> & (2-Phenyl-4-

pyrimidinyl)-S-methyl-isothio-</RTI> urea hydraulic iodide of the F. 2200 < RTI ID=32.12> (Zers.) < /RTI> Example 19: 22.8 g n (2-Phenyl-4-pyrimidinyl) - S-methyl-isothioharnstoff-hydrojodid (starting material of example 18) and 9.4 g propylene diamine (1,3-Diaminopropan) are warmed up in 300 ml methanol 6 hours under agitating and return flow. One steams in the rotary evaporator to dry ones, distributes the oily residue between 300 ml water and 300 ml chloroform, dries and evaporates the organic phase and brings her with 50 ml ethyl acetates and 25 ml ethers to the crystallization.

Das erhaltene <RTI ID=33.1>2-C(2-Pheny1-4-pyrimidinyl)-amino]-1,4,5,6-tetrahydro-</RTI> pyrimidin schmilzt bei <RTI ID=33.2>166-1690.</RTI>

From this cousin the mono hydrochloride of the F becomes in acetone with 1 Aequivelant äthanolischer hydrochloric acid. < RTI ID=33.3> 255C< /RTI> < RTI ID=33.4> (Sinters: < /RTI> < off; RTI ID=33.5> 246) < /RTI> erhalten.

Example 20: Eine Lösung von 44,1 g des Hydrojodids von N-(2-Methyl5-pyrimidinyl)-S-methyl-isothioharnstoff und 17,6 g Aethylendiamin in 400 ml absolutem Aethanol wird während 12 Stunden unter Rückfluss gekocht. Nach Filtration und Eindampfen zur Trockne verteilt man den öligen Rückstand zwischen 400 ml Chloroform und ca. 325 ml einer halbgesättigten Sodalösung, trennt die Schichten und extrahiert nachträglich die wässrige Schicht mehrmals mit Chloroform. Die vereinigten Chloroform-Extrakte ergeben nach Trocknen und Einengen beim Versetzen mit Petroläther einen kristallinen Niederschlag des <RTI ID=33.6>2-(2-Methyl-5-</RTI> < RTI ID=33.7> pyrimidinyl) - amino I-2-imidazolins< /RTI> vom F. <RTI ID=33.8>187-189 .</RTI>

Eine durch Erwärmen hergestellte Lösung von 21,3 g der obigen Base in 200 ml Isopropanol und 12,2 g Methansulfonsäure wird langsam mit Aether und wenig Essigester versetzt, worauf allmählich Kristallisation eintritt. Das so erhaltene Methansulfonat des <RTI ID=33.9>2-(2-Methyl-</RTI> < RTI ID=33.10> 5-pyrimidinyl) - amino} 2-imidazolins< /RTI> schmilzt nach dem Umkristallisieren aus einem Gemisch von Methanol und Aceton bei <RTI ID=33.11>149-151".</RTI>

Das als Ausgangsstoff verwendete Hydrojodid des N-(2-Methyl-5 <RTI ID=33.12>pyrimidinyl)-S-methyl-isothioharnstoffs</RTI> kann wie folgt hergestellt werden:
Eine Lösung von 26,5 g 2-Methyl-5-amino-pyrimidin in 750 ml Chloroform wird bei Raumtemperatur tropfenweise mit ca. 42 g Aethoxycarbonyl-isothiocyanat versetzt und das Gemisch danach während 1 Stunde bei Raumtemperatur und 2 1/2 Stunden unter Rückfluss gerührt.

Nach dem Eindampfen zur Trockne kristallisiert man den festen Rückstand aus siedendem absolutem Aethanol um. Man erhält so den N-(2 <RTI ID=33.13>Methyl-5-pyrimidinyl)-N1-äthoxycarbonyl-thioharnstoff</RTI> vom F. 183 <RTI ID=33.14>185".</RTI>

53 g des so erhältlichen <RTI ID=34.1>N-(2-Methyl-5-pyrimidinyl)-N'-äthoxy-</RTI> <RTI ID=34.2>carbonylthioharnstoffs</RTI> werden mit 390 ml einer l-n wässrigen Natriumhydroxidlösung versetzt. Man kocht die entstandene Lösung während 3 Stunden unter Rückfluss, kühlt ab und stellt den pH-Wert durch Zugabe von 6-n Salzsäure auf ca. 8 ein, worauf der <RTI ID=34.3>N-(2-Methyl-;-pyrimidinyl)-</RTI> thioharnstoff auskristallisiert, welcher nach dem Umkristallisieren aus siedendem absolutem Aethanol bei <RTI ID=34.4>191-193 </RTI> unter Zersetzung schmilzt.

Eine Suspension von 28,75 g des obigen N-(2-Methyl-5-pyrimidinyl)thioharnstoffs und 113 g Methyljodid in 1400 ml Aceton wird zum Rückfluss erhitzt, wobei das Ausgangsmaterial in Lösung geht. Ca. 20 Minuten später fallen Kristalle aus. Man kocht noch 1 3/4 Stunde weiter, kühlt auf <RTI ID=34.5>Raustemperatur,</RTI> nutscht das Hydrojodid des N-(2-Methyl-5pyrimidinyl)-S-methyl-isothioharnstoffs ab und wäscht mit wenig Aceton und Aether nach. F. ca. <RTI ID=34.6>152 </RTI> unter Zersetzung.

Aus der Mutter lauge kann beim Einengen im Vakuum eine weitere Menge des kristallinen Hydrojodids erhalten werden.

Beispiel 21: In analoger Weise erhält man: a) aus dem N-(5-Pyrimidinyl)-N -äthoxycarbonyl-thioharnstoff, F. 191 <RTI ID=34.7>1934</RTI> das <RTI ID=34.8>2-[(5-Pyrimidinyl)-amino]-2-imidazolin</RTI> vom Schmelzpunkt <RTI ID=34.9>232-234 ;</RTI> das Hydrochlorid schmilzt bei <RTI ID=34.10>241-243a</RTI> (Zers.); b) aus dem <RTI ID=34.11>N-(2-n-Butyl-5-pyrimidinyl)-N -äthoxycarbonyl-thioharn-</RTI> stoff, F. <RTI ID=34.12>134-1354</RTI> das 2-[(2-n-Butyl-5-pyrimidinyl)-5-amino]-2-imidazolin vom Schmelzpunkt <RTI ID=34.13>145-147 ;</RTI> das Methansulfat schmilzt bei <RTI ID=34.14>100-102";</RTI> <RTI ID=34.15>
1 3 c) aus dem N -(2-Phenyl- 5-pyrimidinyl)-N -äthoxycarbonyl-thioharn-</RTI> stoff, F. <RTI ID=34.16>195-1980</RTI> das 2-[(2-Phenyl-5-pyrimidinyl)-amino]-2-imidazolin vom Schmelzpunkt <RTI ID=34.17>250-252 ;</RTI> das Hydrochlorid schmilzt bei <RTI ID=34.18>230-2334; ;</RTI> <RTI ID=34.19> 4 aus d) aus dem N-[(6-Chlor-2-(4-morpholino)-4-pyrimidinyl]-N-äthoxyearbo-</RTI> nyl-thioharnstoff, F. 185-189 das 2-[(6-Chlor-2-(4-morpholino)-4-pyri <RTI ID=34.20>midinyl)-amino]-2-imidazolin</RTI> vom Schmelzpunkt <RTI ID=34.21>250-252";</RTI> das <RTI ID=34.22>Hydrochlo-</RTI> rid schmilzt bei <RTI ID=34.23>274275C.</RTI>

Beispiel 22: Zu einer Suspension von 18 g N-(2-Dimethylamino-6-methyl-4pyrimidinyl)-S-methyl-isothioharnstoff-hydrojodid in 180 ml Aethanol gibt man 6,12 g Aethylendiamin, wobei eine klare Lösung entsteht. Anschliessend wird während 6 Stunden am Rückfluss gekocht. Das schon während der Reaktion ausgefallene Reaktionsprodukt wird abgenutscht und mit Isopropanol und Aether gewaschen. Das so erhaltene 2-[(2-Dimethyl <RTI ID=35.1>amino-6-methyl-4-pyrimidinyl)-amino]-2-imidazolin</RTI> schmilzt bei <RTI ID=35.2>280-283 .</RTI>

Zu einer Suspension von 10,35 g dieser Base in 300 ml <RTI ID=35.3>abs. Aetha-</RTI> nol gibt man 4,6 g Methansulfonsäure und erwärmt auf dem Wasserbad, wobei eine klare Lösung entsteht. Man dampft zur Hälfte ein und gibt sukzessive 175 ml Aether zu, wobei sich das Methansulfonat vom F: <RTI ID=35.4>226-2280</RTI> ausscheidet.

Der als Ausgangsstoff verwendete Isothioharnstoff wird analog zu Beispiel 6 gewonnen:
4-Amino-2-dimethylamino-6-methyl-pyrimidin werden mit 11,15 g Aethoxy-carbonyl-isothiocyanat in 200 ml abs. Tetrahydrofuran unter Rückfluss <RTI ID=35.5>zum</RTI> <RTI ID=35.6>N-(2-Dimethylamino-6-methyl-4-pyrimidinyl)-N -äthoxy-</RTI> carbonyl-thioharnstoff vom F: <RTI ID=35.7>199-201 </RTI> umgesetzt.

This connection is cooked for ethanol with 180 ml sodium hydroxide solution and 100 ml during 2 hours at the return flow. One restricts in the vacuum and places with 2-n. Hydrochloric acid on pH = 7.5 and nutscht the crystal mash off. Nach Umkristallisieren aus siedendem Alkohol schmilzt der so erhaltene <RTI ID=35.8>N- (2-Dimethylamino-6-methyl-4-pyrimidinyl)-thioharnstoff</RTI> with < RTI ID=35.9> 241-243. < /RTI>

< RTI ID=35.10> 10; 9< /RTI> g of this thiourea are suspended in 1,2 1 acetone and shifted with 29,5 g methyl iodide. With heating up under return flow the suspension goes into solution and crystallizes briefly thereafter. One cooks still another one hour at the return flow and nutscht the crystalline Precipitation < RTI ID=36.1> N (2-Dimethylamino-6-methyl-4-pyrimidinyl) - S-methyl-ISO-< /RTI> thiourea hydraulic iodide of the F: < RTI ID=36.2> 211-2140< /RTI> off.

Beispiel 23: To a solution of 2,1 g ethylen diamine in 40 ml one gives methanol in a portion < RTI ID=36.3> 6,4gN (2-Diäthylamino-5-pyrimidinyl) - S-< /RTI> < RTI ID=36.4> methyl isothioharnstoff hydroj odid< /RTI> and cooks afterwards during 6 hours at the return flow. The yellow reaction solution is evaporated under decreased pressure. Den Rückstand versetzt man mit 75 ml 2-n Natronlauge und schüttelt mit Petroläther zur Entfernung des 5-Amino2-dimethylamino-pyrimidina aus. The aqueous-oily coating is extracted several times with ethyl acetate. From the evaporated ethyl acetate excerpts one keeps < after recrystallizing from ethyl acetate; RTI ID=36.5> 2 [(2-Diäthylamino-5-pyrimidinyl) - amino] - 2-imidazolin< /RTI> of the F: < RTI ID=36.6> 169-171 ". < /RTI>

1.1 g of in such a way received cousin are solved in 35 ml isopropanol and shifted with 0,94 g methane-sulfone-acidic. On additive of ether crystallizes the-methansulfonat from the F: < RTI ID=36.7> 144-1470< /RTI> out.

The isothiourea used as starting material is manufactured as follows:
To a solution of 12,4 g sodium in 360 ml one gives 29.2 g to ethanol < RTI ID=36.8> N, N-Diäthyl-guanidin-hemisulfat< /RTI> and 28.5 g malonic acid more diäthylester and cooks during 3 hours at the return flow. Subsequently, the reaction mixture is evaporated. The residue loosens one in 400 ml water and places with konz. Salzsäure auf pH-3,5, worauf das 2-Diäthylamino4,6-dihydroxy-pyrimidin vom F: < RTI ID=36.9> 235-240 (decomposition) < /RTI> precipitates.

To 25 ml fuming nitric acid (D = 1.52) one drips under agitating at an interior temperature of < RTI ID=36.10> 15-18 < /RTI> within 25 minutes of 65 ml glacial acetic acid. Anschliessend gibt man portionenweise unter gutem Rühren innerhalb 15 Minuten 21 g <RTI ID=36.11>2-Diäthylamino-4,6-dihydroxy-pyrimidin</RTI> too.

After terminated addition still 2 hours at ambient temperature one further-agitates. One pours the reaction mixture on egg and nutscht the failed < RTI ID=36.12> 2-Diäthylamino-4, 6-dihydroxy-5-nitro-pyrimidin< /RTI> of the F: < RTI ID=37.1> 280-282 < /RTI> (Decomposition) off.

25.1 g 2-Diäthylamino-4,6-dihydroxy-5-nitro-pyrimidin are cooked in 150 ml Phosphoroxychlorid and 38 ml Diäthylanilin during 90 minutes at the return flow. The black reaction solution is strongly restricted under decreased pressure. Den öligen Rückstand giesst man auf Eis und extrahiert mit Aether. Den aus den Aetherphasen erhaltenen Rückstand kristallisiert man aus Cyclohexan um. Man erhält so das 2-Di äthylamino-4,6-dichlor-5-nitro-pyrimidin vom F: < RTI ID=37.2> 91-93. < /RTI>

24.5 g < RTI ID=37.3> 2-Eiäthylamino-4,6-dichlor-5-nitro-pyrim< /RTI> werden in 250 ml Aethanol mit 12 g Raneynickel als Katalysator hydriert. After admission of 3 mol equivalents hydrogen is filtered off by the catalyst and the filtrate with 8-n of alcoholic hydrochloric acid is more acidic placed.

Anschliessend engt man unter vermindertem Druck stark ein bis zu beginnenden Kristallisation. Man nutscht die Kristalle ab und erhält so das 2-Diäthylamino-4,6-dichlor-5-amino-pyrimidin-dihydrochlorid.

20,5 g <RTI ID=37.4>2-Diäthylamino-4, 6-dichlor-5-amino-pyrimidin-dihydrochlo-</RTI> rid hydrogenated in 600 ml ethanol with 2 g palladium-carburize (5% industrial union) as catalyst and 23 gwasserfreiem Natriumacetat at ambient temperature. After admission of 2 mol equivalents one filters hydrogen off from the catalyst and places the failed inorganic salts and the filtrate with surplus 8-normaler alcoholic hydrochloric acid strongly more acidic and evaporates under decreased pressure to the dry one. The oily residue, which contains the 2-Diäthylamino-5-amino-pyrimidindihydrochlorid, cooked for 25 in 250 ml chloroform with 55 g Aethoxycarbonyl isothiocyanat and ml tri ethyl amine during 3 hours at the return flow. The reaction solution is evaporated in the vacuum to dry ones. Den Rückstand chromatographiert man an Silicagel, indem man mit Toluol mit steigendem Essigesterzusatz eluiert.Man erhält so den <RTI ID=37.5>N-(2-Diäthylamino-5-pyrimidinyl)-N -carbäthoxy-thioharnstoff</RTI> of the F: < RTI ID=37.6> 130-1320.< /RTI>

< RTI ID=37.7>
N1 3
7,35 g N -(2-Diäthylamino-5-pyrimidinyl)-N -carbäthoxy-thioharn-</RTI> stoff werden mit 70 ml l-n Natronlauge während 1 Stunde am Rückfluss gekocht. Nach dem Abkühlen wird das Reaktionsgemisch auf pH-8 gestellt.

One nutscht the failed crystals off and recrystallizes from ethyl acetate petroleum ether. One receives so the n (2-Diäthylamino-5-pyrimidinyl) - to thiourea from the F: < RTI ID=38.1> 162-1660C.< /RTI>

4.05 g of the above thiourea are agitated in 25 ml acetone with 8,1 ml methyl iodide during 2 hours under return flow. Die Reaktionslösung wird eingedampft und der Rückstand aus Essigester unter Zusatz von Aether kristallisiert. Man erhält so das N-(2-Diäthyl <RTI ID=38.2>amino-5-pyrimidinyl) S-methyl-isothioharnstoff-hydrojodid</RTI> vom F: <RTI ID=38.3>1751770.</RTI>

Example 24: A mixture of 6,6 g < RTI ID=38.4> 2 [(6-Chlor-2-dimethylamino-5-< /RTI> < RTI ID=38.5> methyl-4-pyrimidinyl) - amino] - 2-imidazolin-hydrochlorid, < /RTI> 200 ml Essigsäure und 30,25 ml 1,5-normaler Salzsäure in Eisessig, wird unter Zusatz von 1,3 g eines 10 <RTI ID=38.6>zeigen</RTI> <RTI ID=38.7>Palladium-Rohle-Katalysators</RTI> bis zur Aufnahme von 1 Moläquivalent Wasserstoff, bei <RTI ID=38.8>35"C</RTI> and 4 bar pressure hydrogenates. Danach wird vom Katalysator abfiltriert und das Filtrat unter vermindertem Druck eingedampft.

Nach Umkristallisation des Rückstandes aus Aethylalkohol, unter Zusatz von Aktivkohle erhält man als farbloses Kristallisat, das <RTI ID=38.9>2-t2-Dimethylamino-5-methyl-4-pyri-</RTI> <RTI ID=38.10>midinyl) -amino 1 -2-imidazolin-hydrochlorid,</RTI> welches bei <RTI ID=38.11>263 </RTI> (Zersetzung) schmilzt.

Der Ausgangsstoff wird gemäss dem Beispiel 29 hergestellt.

BeispieL 25: 5.26 g n (6-Chlor-2-dimethylamino-4-pyrimidinyl) - dithio < RTI ID=38.12> carbaminsäure methylester< /RTI> werden mit 1,3 g Aethylendiamin in 50 ml Acetonitril 8 Stunden am Rückfluss erhitzt. Then the solvent in the vacuum one evaporates and one < as residue the received; RTI ID=38.13> 1 (6-< /RTI> <RTI ID=38.14>Chlor-2-dimethylamino-4-pyrimidinyl)-3-(2-aminoäthyl)-thioharnstoff</RTI> by vaporizing with toluol from still adhering humidity releases.

Das zurückbleibende dunkle Oel wird in 50 ml Diphenyläther 2
Stunden auf 2000 erhitzt. Hierauf wird das Lösungsmittel im Kugelrohr am Vakuum abdestilliert, der halb-kristalline Rückstand mit Wasser verrührt, filtriert und das Produkt mit Wasser und Isopropanol gewaschen.

Das erhaltene <RTI ID=39.1>2-[(6-Chlor-2-dimethylamino-4-pyrimidinyl)-amino]-2-imi-</RTI> dazolin schmilzt bei <RTI ID=39.2>278-279 .</RTI>

Der als Ausgangs stoff verwendete N-(6-Chlor-2-dimethylamino-4pyrimidinyl)-dithiocarbaminsäure-methylester kann auf folgende Weise hergestellt werden: <RTI ID=39.3>8 g</RTI> 4-Amino-5-chlor-2-dimethylamino-pyrimidin are submitted in 100 ml dimethyl formamides. Dazu werden portionenweise während 5 Minuten 2,4 g Natriumhydrid bei <RTI ID=39.4>Oo</RTI> admitted and 15 minutes agitated. Hierauf werden 1,5 ml Schwefelkohlenstoff bei <RTI ID=39.5>0-50</RTI> zugetropft und 30 Minuten nachgerührt. Es wird erneut bei <RTI ID=39.6>0-5 </RTI> 1.2 g sodium hydride admitted, 15 minutes agitated and then at the same temperature 0.75 ml carbon disulphide admitted and 30 minutes further agitated. After renewed addition of 1,2 g sodium hydride and 0.75 ml carbon disulphide in the way described above are < after 30 minutes with; RTI ID=39.7> 0-50< /RTI> 2,8 ml methyl iodide admitted and the reaction solution in 2 hours on < itself; RTI ID=39.8> 20 < /RTI> erwärmen lassen. Dann wird mit Wasser zersetzt, unlösliches Material abfiltriert und das Filtrat mit 2-normaler Salzsäure auf pH 5-6 gestellt. Das ausgefallene Produkt wird mit Methylenchlorid ausgezogen, getrocknet und eingedampft, worauf der N-(6-Chlor-2-dimethylamino-4-pyrimidinyl)-dithiocarbaminsäure-methylester bei Zugabe von Aether auskristallisiert und abfiltriert wird. F: <RTI ID=39.9>150-151".</RTI>

Example. 26: 38 g <RTI ID=39.10>6-Chlor-2-dimethylamino-4-(dimethylthio-methylen-</RTI> imino)-pyrimidin und 9,2 ml Aethylendiamin in 400 ml Methanol werden 14 Stunden bei <RTI ID=39.11>60 </RTI> gerührt. Das ausgefallene 2-[(6-Chlor-2-dimethyl <RTI ID=39.12>amino-4-pyrimidinyl)-amino]-2-imidazolin</RTI> wird durch Filtration isoliert und schmilzt bei <RTI ID=39.13>278-2790.</RTI>

The basic material is manufactured as follows:
Eine Lösung von 70 g 4-Amino-6-chlor-2-dimethylamino-pyrimidin in 750 ml Dimethylformamid wird unter Stickstoffatmosphäre und Eis Kochsalz-Kühlung portionenweise mit 19,8 g Natriumhydrid (50 % in Oel) versetzt, so dass die Temperatur 100 nicht übersteigt. Es wird noch eine Stunde im Eisbad gekühlt, bis die heftige Wasserstoffentwicklung aufhört. Danach werden 12,3 ml Schwefelkohlenstoff unter Kühlen bei <RTI ID=40.1>0-10 </RTI> zugetropft und diese Temperatur für eine Stunde beibehalten. Nun wird nochmals 9,9 g Natriumhydrid in Portionen bei <RTI ID=40.2>0-10 </RTI> admitted.

Das Reaktionsgemisch wird 30 Minuten im Eisbad gerührt, wonach 6,1 ml Schwefelkohlenstoff bei <RTI ID=40.3>0-10 </RTI> zugetropft werden. Es wird noch eine Stunde unter Eiskühlung nachgerührt, dann wird, wie oben beschrieben, nochmals mit 9,9 g Natriumhydrid und 6,1 ml Schwefelkohlenstoff behandelt. Nach Zugabe des Schwefelkohlenstoffs wird noch eine Stunde im Eisbad gerührt. Nun werden unter Eis-Kochsalz-Kühlung 63,4 ml Methyljodid innerhalb etwa 30 Minuten so zugetropft, dass die Temperatur 150 nicht übersteigt. Anschliessend wird das Kühlbad entfernt und noch 2 Stunden gerührt. Afterwards under ice cooling slowly 200 is course-dripped ml water and the reaction mixture is filled on 2000 ml water. Das ausgefallene Rohprodukt wird abgesaugt, gründlich mit Wasser gewaschen und danach dreimal mi je 1000 ml Cyclohexan ausgekocht.Die vereinigten Cyclohexanextrakte werden über Natriumsulfat getrocknet, filtriert und bis auf ein Volumen von etwa 150 ml eingeengt. When cooling in the ice bath colorless 6-Chlor crystallizes < RTI ID=40.4> 2-dimethylamino-4 (dimethylthio methylenimino) - pyrimidin, welches< /RTI> bei <RTI ID=40.5>85-870</RTI> schmilzt.

In gleicher Weise wird das <RTI ID=40.6>2-[(2,6-Dichlor-4-pyrimidinyl)-amino}</RTI> 2-imidazolin (F: <RTI ID=40.7>215-217)</RTI> aus 4-Amino-2,6-dichlorpyrimidin erhalten.

Das dabei als Zwischenprodukt auftretende 2,6-Dichlor-4-(dimethylthio-methylenimino)-pyrimidin schmilzt bei <RTI ID=40.8>F. 99-1000.</RTI>

Example 27: 4,7 g <RTI ID=40.9>2-[(2,6-Dichlor-4-pyrimidinyl)-amino]-2-imidazolin</RTI> und 7,8 ml alkoholische Dimethylamin-Lösung (33 %) werden in 30 ml Aethanol 90 Minuten unter Rückfluss gekocht. Das ausgefallene <RTI ID=41.1>2-[(6-Chlor-2-dimethylamino-4-pyrimidinyl)-amino]-2-imidazolin</RTI> wird noch heiss abgenutscht und mit Wasser und Aethanol gewaschen. Das Produkt ist mit demjenigen des Beispiels 11 identisch.

Der Ausgangsstoff wird gemäss dem Beispiel 26 hergestellt.

Beispiel 28: Ein Gemisch von 1 g 6-Chlor-2-dimethylamino-4-cyanaminopyrimidin und 0,5 ml Aethylendiamin wird mit einem Tropfen Schwefelkohlenstoff versetzt und 1 Stunde auf <RTI ID=41.2>100"</RTI> erhitzt. Anschliessend engt man das Reaktionsgemisch amRatavapor ein und suspendiert den Rückstand in 50 ml heissem Aethanol. Insoluble 2 [(6-Chlor-2-dimethylamino < RTI ID=41.3> 4-pyrimidinyl) - amino] - 2-imidazolin< /RTI> wird heiss abgenutscht und schmilzt bei <RTI ID=41.4>264-268 .</RTI> After recrystallization from Dimethylsulfoxid methanol rises the melting point to < RTI ID=41.5> 2782790.< /RTI>

Der Ausgangsstoff wird wie folgt hergestellt:
Eine Lösung von 6,3 g 4-Amino-6-chlor-2-dimethylamino-pyrimidin in 60 ml Dimethylformamid wird unter

Stickstoffatomosphäre und Eis Kochsalz-Kühlung portionenweise mit 1,75 g Natriumhydrid (50 % in Oel) versetzt, so dass die Temperatur <RTI ID=41.6>LOO</RTI> nicht übersteigt. Es wird noch 30 Minuten im Eisbad gekühlt, bis die heftige Wasserstoffentwicklung aufhört. Danach tropft man langsam eine Lösung von 3 g Bromcyan in 30 ml Dimethylformamid unter Eiskühlung zu, wobei die Temperatur 200 nicht übersteigen sollte. Nach erfolgter Zugabe rührt man noch 30 Minuten bei <RTI ID=41.7>0-100</RTI> und neutralisiert dann mit 2-normaler Salzsäure.

Das Reaktionsgemisch wird auf 100 ml Eiswasser gegossen und mehrmals mit Essigester extrahiert. Die vereinigten Essigesterextrakte werden mit Natriumsulfat getrocknet und eingeengt. Durch Umkristallisation des Rückstandes aus Aethanol erhält man das kristalline 6-Chlor-2dimethylamino-4-cyanamino-pyrimidin vom F. <RTI ID=41.8>229-2320.</RTI>

Beispiel 29: 2,9 g (0,01 Mol) 6-Chlor-2-dimethylamino-4-(dimethylthio <RTI ID=41.9>methylenimino)-5-methyl-pyrimidin</RTI> <RTI ID=41.10>und 0,6</RTI> g (0,01 Mol) Aethylendiamin werden in 50 ml absolutem Methylalkohol gelöst und 16 Stunden bei 600 gerührt. Danach wird auf Raumtemperatur abgekühlt und das ausgefallene <RTI ID=42.1> 2-[(6-Chlor-2-dimethylamino-5-methyl-4-pyrimidinyl)-Amino]-2-imidazolin</RTI> durch Filtration isoliert. Das Kristallisat suspendiert man in Methylalkohol, säuert an mit 5-normaler methanolischer Salzsäure und dampft die klare Lösung unter vermindertem Druck ein.Nach Umkristallisation des Rückstandes aus Methylalkohol-Diäthyläther, unter Zusatz von Aktivkohle, erhält man als farbloses Kristallisat das 2-[(6-Chlor-2 <RTI ID=42.2> dimethylamino-5-methyl-4-pyrimidinyl)-amino]-2-imidazolin-hydrochlorid,</RTI> welches unter Zersetzung bei 3000 schmilzt.

Der Ausgangsstoff wird wie folgt hergestellt:
Zu einer frischen Natriummethylatlösung, hergestellt aus 12,4 g (0,54 Mol) Natrium und 60 ml absolutem Methylalkohol, gibt man bei 600 Reaktionstemperatur, 36,8 g <RTI ID=42.3>(0,27</RTI> Mol) <RTI ID=42.4>N,N-Dimethylguanidin-hydrogen-</RTI> sulfat, und kocht 20 Minuten unter Rückfluss. Danach wird bei Rückflusstemperatur innert 30 Minuten eine Lösung von 34,4 g <RTI ID=42.5>(0,27</RTI> Mol) <RTI ID=42.6>2-Cyano-propionsäure- thylester</RTI> in 110 ml absolutem Methylalkohol zugetropft, und die weisse Suspension noch eine weitere Stunde gekocht.

Nach Abkühlen des Gemisches, filtriert man ab, und stellt das Filtrat mit 4,5-normaler methanolischer Salzsäure auf pH 5-6 ein. Das ausgefallene Kristallisat wird abfiltriert und mit kaltem Methylalkohol und Diäthyläther gewaschen. Nach dem Trocknen im Hochvakuum bei 700C erhält man als farbloses Kristallisat, das 4-Amino-2-dimethylamino-6 <RTI ID=42.7>hydroxy-5-methyl-pyrimidin-hydrochlorid-monohydrat,</RTI> vom F. <RTI ID=42.8>285-290 .</RTI>

Ein Gemisch von 5,0 g (0,0244 Mol) 4-Amino-2-dimethylamino-6hydroxy-5-methyl-pyrimidin-hydrochlorid, 22,3 ml (0,244 Mol) Phosphoroxychlorid und 2,55 ml (0,0183 Mol) Triäthylamin wird unter Rühren 9 Stunden am Rückfluss gekocht. Danach wird das überschüssige Phosphoroxychlorid unter vermindertem Druck abdestilliert, und das zurückbleibende viskose Oel auf Eiswasser ausgetragen. Reaktionstemperatur bis 500. Nach Abklingen der Reaktion wird noch eine Stunde bei 600C gerührt und danach auf Raumtemperatur abgekühlt. Mit konz.

Sodium hydroxide solution is adjusted to pH 7, and agitated a further hour with 55-600C. Dabei muss der pH Wert durch mehrmaliges Zugeben von konz. Natronlauge korrigiert werden. Dann wird abgekühlt und viermal mit je 40 ml Chloroform extrahiert. Die vereinigten Chloroformextrakte werden mit Natriumsulfat getrocknet und unter vermindertem Druck eingedampft. Nach Umkristallisation des Rückstandes aus Isopropylalkohol, unter Zusatz von Aktivkohle, erhält man als gelbliches Kristallisat, das <RTI ID=43.1>4-Amino-6-chlor-2-dimethylamino-5-methyl-pyrimidin,</RTI> vom F . <RTI ID=43.2>170-1720.</RTI>

Eine Lösung von 2 g (0,0107 Mol) 4-Amino-6-chlor-2-dimethyl <RTI ID=43.3>amino-5-methyl-pyrimidin</RTI> in 20 ml absolutem Dimethylformamid wird unter Stickstoffatmosphäre und Eis-Kochsalz-Kühlung mit 0,33 g (0,0069 Mol) Natriumhydrid (50 % in Oel) versetzt, und eine Stunde bei <RTI ID=43.4>0,5 </RTI> gerührt. Danach werden 0,2 ml (0,0033 Mol) Schwefelkohlenstoff unter Kühlen bei 0,100C zugegeben und diese Temperatur für eine Stunde beibehalten. Nun wird nochmals 0,33 g Natriumhydrid bei <RTI ID=43.5>0-5"</RTI> zugegeben und 30 Minuten bei 00 gerührt, worauf man weitere 0,2 ml Schwefelkohlenstoff beigibt und das Gemisch eine Stunde unter Eiskühlung nachrührt. Dann wird, wie oben beschrieben, nochmals mit 0,34 g Natriumhydrid und 0,25 ml Schwefelkohlenstoff behandelt. Nach der Zugabe des Schwefelkohlenstoffs wird noch eine Stunde im Eisbad gerührt.

Nun werden unter Eis-Kochsalz-Kühlung 1,65 ml <RTI ID=43.6>(0,0267.</RTI> Mol) Methyljodid während etwa 15 Minuten so zugetropft, dass die Temperatur 100 nicht übersteigt. Anschliessend wird das Kühlbad entfernt und noch zwei Stunden aus gerührt.

Danach giesst man das Reaktionsgemisch auf 50 ml Eiswasser und extrahiert dreimal mit je 30 ml Essigester. Die vereinigten Essigesterextrakte werden mit Natriumsulfat getrocknet und unter vermindertem Druck eingedampft. Durch Auskochen des Rückstandes mit Petroläther wird vom Mineralöl befreit. Zur Entfernung von noch anhaftender Feuchtigkeit und Spuren Dimethylformamid, wird mit Toluol behandelt, und man erhält als öligen Rückstand das 6-Chlor-2-dimethylamino-4-(dimethylthio-methylenimino)-5-methyl-pyrimidin, welches direkt als Rohprodukt als Ausgangsstoff verwendet wird.

Gegebenenfalls kann aus Cyclohexan umkristallisiert werden, wobei man ein farbloses Kristallisat, welches bei <RTI ID=44.1>115-117 </RTI> schmilzt, erhält.

Auf gleiche Weise werden auch die folgenden Verbindungen herge <RTI ID=44.2>stellt: 2-[C2-Methylamino-4-pyrimidinyl)-amino]-2-imidazolin.</RTI> Sein Dihydrochlorid schmilzt bei <RTI ID=44.3>275-280".</RTI>

<RTI ID=44.4>2- [(6-Chlor-2-propylamino-4-pyrimidinyl)-amino]-2-imidazolin-hydro-</RTI> chlorid, F. <RTI ID=44.5>230-234 ;</RTI> <RTI ID=44.6>2-[(6-Chlor-2-(N-methyl-N-propyl-amino)-4-pyrimidinyl)-aminol-2-</RTI> <RTI ID=44.7>imidazolin-hydrochlorid,</RTI> F. <RTI ID=44.8>187-1890;</RTI> <RTI ID=44.9>2- [(2-Propylamino-4-pyrimidinyl)-amino]-2-imidazolin,</RTI> F. <RTI ID=44.10>230-233 .</RTI>

Das als Ausgangsstoff verwendete <RTI ID=44.11>4-Amino-6-chlor-2-propylamino-</RTI> pyrimidin kann auf folgende Weise hergestellt werden:
Ein Gemisch von 12,3 g 4-Amino-2,6-dichlor-pyrimidin und 16,4 ml n-Propylamin in 700 ml Methylalkohol, wird unter Rühren zum Rückfluss erwärmt, und die bald klare Lösung weitere 16 Stunden gekocht. Danach wird unter

vermindertem Druck zur Trockene eingedampft. Den Rückstand stellt man mit 2-normaler Natriumcarbonatlösung alkalisch und extrahiert mehrmals mit Chloroform. Die vereinigten Chloroformextrakte werden mit Natriumsulfat getrocknet und eingedampft. Nach Kristallisation des Rückstandes aus Petroläther filtriert man ab, und erhält auf diese Weise, das <RTI ID=44.12>4-Amino-6-chlor-2-propylamino-pyrimidin</RTI> vom F. <RTI ID=44.13>85-90 .</RTI>

Das als Ausgangsstoff verwendete 4-Amino-6-chlor-2-(N-methyl-Npropyl-amino)-pyrimidin kann auf die gleiche Weise wie das zuvor beschriebene 4-Amino-6-chlor-2-propylamino-pyrimidin hergestellt werden, indem man N-Methyl-N-propylamin anstatt n-Propylamin zur Reaktion einsetzt. Das auf diese Art erhaltene 4-Amino-6-chlor-2-(N-methyl-Npropyl-amino)-pyrimidin wird als Rohprodukt zur folgenden Stufe angesetzt.

Das als Ausgangsstoff verwendete 4-Amino-2-propylamino-pyrimidin kann nach folgendem Verfahren hergestellt werden:
Ein Gemisch von 3,7 g <RTI ID=45.1>4-Amino-6-chlor-2-propylamino-pyrimidin,</RTI> 140 ml Eisessig und 30 ml 2N Salzsäure wird unter Zusatz von 0,7 g eines 10 %igen Palladium-Kohle-Katalysators bis zur Aufnahme von 1 Moläquivalent Wasserstoff bei Raumtemperatur und 4 bar Druck hydriert.

Danach wird vom Katalysator abfiltriert und das Filtrat unter vermindertem Druck eingedampft. Den Rückstand stellt man unter Zusatz von Eis, mit 2-normaler Natriumcarbonatlösung alkalisch und extrahiert mehrmals mit Chloroform. Die vereinigten Chloroformextrakte werden mit Natriumsulfat getrocknet und unter vermindertem Druck eingedampft.

Das zurückbleibende <RTI ID=45.2>4-Amino-2-propylamino-pyrimidin</RTI> wird ohne weitere Reinigung zur folgenden Stufe eingesetzt.

Beispiel 30: Analog zu den in den vorhergehenden Beispielen beschriebenen Methoden werden auch die folgenden Verbindungen hergestellt: <RTI ID=45.3>2-[(2,6-Diäthoxy-4-pyrimidinyl)-amino]-2-imidazolin,</RTI> F. <RTI ID=45.4>193-1950;</RTI> <RTI ID=45.5>2-f(2-Dimethylamino-6-methoxy-4-pyrimidinyl)-amino]-2-imidazolin,</RTI> F. <RTI ID=45.6>9092C;</RTI> <RTI ID=45.7>2-[(2-Isopropoxy-6-methoxy-4-pyrimidinyl)-amino]-2-imidazolin,</RTI> F. <RTI ID=45.8>209-2104;</RTI> <RTI ID=45.9>2-[C2-Butoxy-6-methoxy-4-pyrimidiny1)-amino-2-imidazo1in,</RTI> F. <RTI ID=45.10>184-185 ;</RTI> 2-[(6-Chlor-2-isopropoxy-4-pyrimidinyl)-amino]-2-imidazolin, F <RTI ID=45.11>210-2110;;</RTI> <RTI ID=45.12>2-[C2,6-Bis-dimethylamino-4-pyrimidinyl)-amino]-2-imidazolin,</RTI> F. 310-3120 und das <RTI ID=45.13>2-[(2-Isopropoxy-4-pyrimidinyl)-amino]-2-imidazolin.</RTI> F. <RTI ID=45.14>261-263 .</RTI>

Die Ausgangsstoffe werden wir folgt hergestellt:
11,5 g (0,5 Mol) Natrium werden in 400 ml absol. Alkohol gelöst, unter Rühren zum Kochen erhitzt und portionenweise in ca. 20 Minuten 32,8 g (0,2 Mol) 4-Amino-2,6-dichlor-pyrimidin zugegeben. Man kocht danach noch 8 Stunden, filtriert und dampft das Filtrat unter vermindertem Druck ein. Der Rückstand wird mit Wasser angerieben, filtriert und aus Alkohol umkristallisiert. Man erhält das 4-Amino-2,6-diäthoxypyrimidin, welches bei <RTI ID=46.1>106-108- -</RTI> schmilzt.

32,8 g (0,2 Mol) <RTI ID=46.2>4-Amino-2,6-dichlor-pyrimidin,</RTI> 400 ml i-Propanol und eine Lösung von 4,6 g (0,2 Mol) Natrium in 100 ml i-Propanol werden 15 Stunden am Rückfluss gekocht. Man dampft unter vermindertem Druck ein, reibt den Rückstand mit Wasser an und erhält durch Filtrieren ein Rohprodukt, welches bei <RTI ID=46.3>108-112 </RTI> schmilzt. Nach Umkristallisieren aus i-Propanol erhält man das 4-Amino-6-chlor-2-iso <RTI ID=46.4>propoxy-pyrimidin,</RTI> welches bei <RTI ID=46.5>125-1270</RTI> schmilzt.

18,8 g <RTI ID=46.6>(0,1 Mol)</RTI> der letztgenannten Verbindung werden 8 Stunden mit einer Lösung von 2,3 g (0,1 Mol) Natrium in 100 ml Methanol gekocht. Man filtriert und dampf das Filtrat unter vermindertem Druck ein. Der Rückstand wird mit Wasser angerieben, filtriert und aus Methanol umkristallisiert. Man erhält das 4-Amino-2-isopropoxy-6methoxy-pyrimidin, welches bei <RTI ID=46.7>89-900</RTI> schmilzt.

Anstelle der gereinigten Verbindung kann auch das oben beschriebene Rohprodukt, welches bei <RTI ID=46.8>108-112 </RTI> schmilzt, verwendet werden.

In analoger Weise wird auch das 4-Amino-2-n-butoxy-6-methoxypyrimidin, welches bei <RTI ID=46.9>94-96 </RTI> schmilzt, hergestellt.

Die erhaltenen 4-Aminoverbindungen können z.B. gemäss Beispiel 1 in die entsprechenden <RTI ID=46.10>S-Methyl-isothioharns tof f-Verbindungen</RTI> umgewandelt werden. Ihre Umsetzung mit Aethylendiamin ergibt die entsprechen den Imidazolin-Produkte.

Beispiel 31: Analog zu den in den vorhergehenden Beispielen, z.B. gemäss den Beispielen 11 und 13, werden auch die folgenden Verbindungen hergestellt:
2-[(2-Methyl-6-phenylamino-4-pyrimidinyl)-amino]-2-imidazolin.

F. <RTI ID=47.1>263-265 .</RTI> Das Hydrochlorid schmilzt bei <RTI ID=47.2>311-3130.</RTI>

<RTI ID=47.3> 2-f(6-(4-Methoxy-phenyl)-amino-2-methyl-4-pyrimidinyl)-aminof-2-</RTI> imidazolin. F. <RTI ID=47.4>266-269 .</RTI> Das Hydrochlorid schmilzt bei <RTI ID=47.5>281-283 .</RTI>

<RTI ID=47.6> 2-[(6-(4-Chlor-phenyl)-amino-2-methyl-4-pyrimidinyl)-amino]-</RTI> 2-imidazolin. F. <RTI ID=47.7>282-2840.</RTI> Das Hydrochlorid schmilzt bei <RTI ID=47.8>320-322a.</RTI>

<RTI ID=47.9> 2-[(2-Methyl-6-phenoxv-4-pyrimidinyl)-amino]-2-imidazolin. Das</RTI> Hydrochlorid schmilzt bei <RTI ID=47.10>302-305 .</RTI>

Die als Ausgangsstoffe verwendeten neuen Verbindungen und ihre neuen Vorstufen werden z.B. analog zu denjenigen der Beispiele 11 oder 13 wie folgt hergestellt: Ad 1): Ausgehend von 4-Amino-6-chlor-2-methyl-pyrimidin und Anilin erhält man das- 4-Amino-2-methyl-6-phenylamino-pyrimidin, F. < RTI ID=47.11> 192-1940.< /RTI>

Dieses ergibt nach Umsetzung mit Aethoxycarbonyl-isothiocyanat den entsprechenden Aethoxycarbonyl-thioharnstoff <RTI ID=47.12>(F,199-2000),</RTI> der mit l-normaler Natriumhydroxydlösung zum entsprechenden Thioharnstoff

verseift wird (F. <RTI ID=47.13>227-230).</RTI> Die Umsetzung dieses Thioharnstoffs mit Methyljodid ergibt den als Ausgangsstoff verwendeten N-(2-Methyl <RTI ID=47.14>6-phenylamino-4-pyrimidinyl)-S-methyl-isothioharnstoff-hydrojodid,</RTI> welches bei ungefähr <RTI ID=47.15>150 </RTI> schmilzt.

Ad 2): Ausgehend von 4-Amino-6-chlor-2-methyl-pyrimidin und p-Anisidin erhält man das <RTI ID=47.16>4-Amino-6-(4-methoxyphenyl)-amino-2-methyl-pyrimidin,</RTI> F. <RTI ID=47.17>243-2450.</RTI> Dieses ergibt nach Umsetzung mit Aethoxycarbonyl-isothio cyanat in Aceton und Dimethylformamid den entsprechenden Aethoxycarbonyl-thioharnstoff (F. <RTI ID=48.1>198-200),</RTI> der mit 1-normaler Natriumhydroxydlösung zum entsprechenden Thioharnstoff verseift wird. (F <RTI ID=48.2>221-2240).</RTI>

Die Umsetzung dieses Thioharnstoffes mit Methyljodid in Methanol-Dimethylformamid ergibt den als Ausgangsstoff verwendeten N-[6-(4 <RTI ID=48.3>methoxy-phenyl)-amino-2-methyl- 4-pyrimidinyl] -Smethyl-isothio-</RTI> harnstoff-hydrojodid, welches bei <RTI ID=48.4>165-167 </RTI> schmilzt.

Ad 3): Ausgehend von <RTI ID=48.5>4-Amino-6-chlor-2-methyl-pyrimidin</RTI> und p-Chloranilin erhält man das 4-Amino-6-(4-chlorphenyl)-amino-2-methyl-pyrimidin, F. <RTI ID=48.6>180-1820.</RTI> Dieses ergibt nach Umsetzung mit Aethoxycarbonylisothiocyanat in Aceton und Dimethylformamid den entsprechenden Aethoxycarbonyl-thioharnstoff (F. <RTI ID=48.7>200-2020),</RTI> with 2-normaler the sodium hydroxide solution to the appropriate thiourea is soaped (F. < RTI ID=48.8> 242-245 " < /RTI> under decomposition). Die Umsetzung dieses Thioharnstoffes mit Methyljodid in Aceton ergibt den als Ausgangsstoff verwendeten <RTI ID=48.9>N-[6-(4-chlorphenyl)-amino-2-methyl-4-pyrimidinyl]-S-methyl-isothio-</RTI> urea hydraulic iodide, which < with; RTI ID=48.10> 212-215 < /RTI> melts.

Ad 4): Ausgehend von 4-Amino-6-chlor-2-methyl-pyrimidin und Phenolnatrium erhält man das 4-Amino-2-methyl-6-phenoxy-pyrimidin <RTI ID=48.11>(F.165-167).</RTI>

This results in the appropriate Aethoxycarbonyl thiourea (F after conversion with Aethoxycarbonyl isothiocyanat in acetone. < RTI ID=48.12> 139-141) < /RTI> with I-normal sodium hydroxide solution to the appropriate thiourea one soaps (F. < RTI ID=48.13> 221-2240). < /RTI> The conversion of the latter connection with methyl iodide to methanol dimethyl formamides results in as basic material used < RTI ID=48.14> N (2-Methyl-6-phenoxy-4-pyrimidinyl) - < /RTI> S-methyl-isothioharnstoff-hydrojodid.

Example 32: Analog zu den in den vorhergehenden Beispielen beschriebenen Methoden werden auch die folgenden Verbindungen hergestellt: < RTI ID=48.15> 2-t (4-Pyrimidinyl) - amino] - 2-imidazolin.< /RTI>

< RTI ID=49.1> 2 [(2-Butylamino-4-pyrimidinyl) - amino] - 2-imidazolin.< /RTI>

Example 33: Tabletten enthaltend 0,1 g des Hydrochlorids von 2-[(2,6-Dimethyl-4-pyrimidinyl)-amino]-2-imidazolin, können wie folgt hergestellt werden: Composition (for 1000 tablets): 2 [(2,6-Dimethyl-4-pyrimidinyl) - amino] - 2-imidazolin hydrochloride 100.0 g lactose 50.0 g wheat strength 73.0 g colloidal silicic acid 13.0 g magnesium stearate 2.0 g talc < RTI ID=49.2> 12,0 g< /RTI> Wasser <RTI ID=49.3>q.s.</RTI>

2 [(2,6-Dimethyl-4-pyrimidinyl) - revision modification NO] - 2-imidazolin-hydrochlorid is mixed with a part of the wheat strength, with the lactose and the colloidal silicic acid and the mixture by a screen is driven.

A further part of the wheat strength is angeknetet with the 5-fold quantity water on the water bath lining ice third and the above powder substance with this Kleister, until a weakly plastic < RTI ID=49.4> Masse< /RTI> entsteht. Diese wird durch ein Sieb von 3 mm <RTI ID=49.5>Maschenweite</RTI> printed, dried and the dry granular material again by a screen floated. Whereupon becomes the remaining wheat strength, which talc and the magnesium stearate inject added and the received mixture to tablets of 0,25 g.

In analog way become also tablets or other pharmaceutical preparations, which another connection of the invention, e.g.

such of the preceding examples contain, manufactured.

Patentansprüche (für alle benannten Länder ausser Oesterreich) 1. 2 (Pyrimidinylamino) - 1,3-diaza-2-cycloalken-Verbindungen of the general formula < RTI ID=50.1> 1</RTI>
EMI50.1
where Py if necessary substituted 4 connected by a carbon atom with the nitrogen atom - or 5-Pyrimidinylrest < RTI ID=50.2> represent, < /RTI> G 1 and R2 independently hydrogen, Niederalkyl or Niederalkenyl mean, and alkene for Niederalkylen stands, which separates the two nitrogen atoms by 2 to 4 carbon atoms, for their tautomere connections and acidic addition salts.

2. Bonds of the formula I, where Py for if necessary equal by one, two or three or different substituents of the group of Niederalkyl, Hydroxy, Niederalkoxy, Niederalkylthio, halogen, tri fluorine methyl, Niederalkylsulfonyl, Amino, if necessary by Niederalkyl, Niederalkoxy, Hydroxy, Amino, Niederalkylamino, Diniederalkylamino or halogen substituted Phenyl, Phenoxy or Phenylamino, Niederalkylamino, Dinieralkylamino, Pyrrolidino, Piperidino, Morpholino, Thiomorpholino, Niederalkanoylamino, Niederalkoxycarbonylamino, Ureido, 3-Niederalkylureido and 3,3-Diniederalkylureido substituted, over a carbon atom with the nitrogen atom connected 4 - or 5-Pyrimidinyl stands, shown in the claim 1, g 1 and R2 independently hydrogen, Niederalkyl or Niederalkenyl mean, and, that stands for alkene for Niederalkylen the two nitrogen atoms by 2 to 4 carbon atoms separates, whereby with ?down? designated remainders up to 4 carbon atom containing, their tautomeren connections and Säureaddtionssalze.

3. Verbindungen der im Anspruch 1 gezeigten Formel I, worin Py für gegebenenfalls durch einen, zwei oder drei gleiche oder verschiedene Substituenten der Gruppe Niederalkyl, Hydroxy, Niederalkoxy, Halogen, Amino, gegebenenfalls durch Niederalkyl, Niederalkoxy, Hydroxy, Amino, Niederalkylamino, Diniederalkylamino oder Halogen substituiertes Phenyl, <RTI ID=51.1> Niederalkylamino, Diniederalkylaminos Pyrrolidino, Piperidino, Morpholino, < /RTI> Thiomorpholino, Niederalkanoylamino, <RTI ID=51.2>Niederalkoxycarbonylamino,</RTI> Ureido, 3-Niederalkylureido and 3,3-Diniederalkylureido substituted, over a carbon atom with the nitrogen atom connected 4 - or 5-Pyrimidinyl stands, g 1 and R2 independently for hydrogen, Niederalkyl or Niederalkenyl means, and for alkene for Niederalkylen it stands which separates the two nitrogen atoms by 2 to 4 carbon atoms, whereby with ?down? designated remainders up to 4 carbon

atoms contain, their tautomere connections and acidic addition salts.

4. Connections of the formula I, where Py for if necessary equal to the group of Niederalkyl, Niederalkoxy, Phenyl, Amino, Niederalkylamino, Diniederalkylamino or Morpholino and/or halogen substituted, over a carbon atom with the nitrogen atom connected 4 by one, two or three or different substituents - or 5-Pyrimidinyl stands, shown in the claim 1, g 1 hydrogen or Niederalkyl and R2 hydrogen or Niederalkyl represent, and for alkene for Niederalkylen stands, which separates the two nitrogen atoms by 2 to 3 carbon atoms, whereby with ?down? designated remainders up to 4 carbons < RTI ID=51.3> material-atomiccontain, < /RTI> und Halogen ein Atomgewicht bis zu 35 aufweist, und ihre Säureadditionssalze.

5. Verbindungen der allgemeinen Formel II
EMI51.1
where Alk' stands for Niederalkylen with up to 4 carbon atoms, which separates the two nitrogen atoms by 2 to 3 carbon atoms, and each of the remainders of R3, R4 and R5 hydrogen, Niederalkyl with up to 4 carbon atoms or Niederalkoxy with up to 4 carbon atoms, halogen, Diniederalkylamino, Morpholino or Phenyl, means, and their acidic addition salts.

6. Connections of the general formula III
EMI52.1
worin <RTI ID=52.1>R;</RTI> and R' independently for hydrogen, Niederalkyl < RTI ID=52.2> 3 4< /RTI> mit bis zu 4 Kohlenstoffatomen oder Niederalkoxy mit bis zu 4 Kohlenstoffatomen, Halogen oder Diniederalkylamino stehen, und n für 1 oder 2 steht, und ihre Säureaddtionssalze.

7. 2 [(6-Chlor-2-dimethylamino-4-pyrimidinyl) - amino] - 2-imidazolin and its acidic addition salts 8. <RTI ID=52.3>2-[C6-Chlor-2-diäthylamino-4-pyrimidinyl)-amino]-2-imidazolin</RTI> und seine Säureadditionssalze.

9. 2-[(6-Chlor-2-(4-morpholino)-4-pyrimidinyl)-amino]-2-imidazolin und seine Säureadditionssalze.

10. Hypotensiv and antihypertensiv effective in accordance with connections < RTI ID=52.4> Anspruch 1 > their tautomere connections and their Säureadditionssalze.< /RTI>

11. <RTI ID=52.5>Hypotensiv</RTI> und antihypertensiv wirksame Verbindungen gemäss Anspruch 2, deren tautomere Verbindungen und ihre Säureadditionssalze.

12. Pharmazeutische Präparate enthaltend Verbindungen gemäss einem der Ansprüche 1 und 3 bis 10 oder therapeutisch verwendbare Säureadditionssalze von solchen Verbindungen.

13. Pharmaceutical preparations containing bonds in accordance with one of the claims of 2 and 11 or therapeutically usable acidic addition salts of such connections.

14. The connections of the claims < RTI ID=53.1> I< /RTI> and 3 to 10 to the use as pharmaceutical products.

15. Die Verbindungen der Ansprüche 2 und 11 zur Verwendung als Pharmazeutika.

16. The connections of the claims 1 and 3 to 10 to the use in methods to the therapeutic treatment of the human or animal body.

17. The connections of the claims 2 and 11 to the use in a method to the therapeutic treatment of the human or animal body.

18. Method to the preparation of new 2 (Pyrimidinylamino) - 1,3diaza-2-cycloalken-Verbindungen of the general formula I
EMI53.1
where Py if necessary substituted 4 connected by a carbon atom with the nitrogen atom - or 5-Pyrimidinylrest represents, g 1 and R2 independently hydrogen, Niederalkyl or Niederalkenyl mean, and alkene for Niederalkylen stands, which separates the two nitrogen atoms by 2 to 4 carbon atoms, for their tautomeren bonds and acidic addition salts of it, characterised in that one A) a connection of the formula Py-x (IV) or a salt of it with a connection of the formula
EMI54.1
or a salt of the fact it converts where one of the remainders of X and Y an amino group of the formula - N (R2) - H < RTI ID=54.1> (VI) < /RTI> represents, and the other one a group split offable on the reaction conditions as well as hydrogen means, or b) a connection of the formula VII
EMI54.2
worin <RTI ID=54.2>Yl</RTI> the Iminogruppe, a split offable group, which mean Oxo or Thioxogruppe, and Y2 a split offable group or Y1 and a Y2 collected a triple bound nitrogen atom mean, if R2 has the meaning of hydrogen, or the appropriate tautomere form, or a salt of it, with an alkyl diamine connection of the formula < RTI ID=54.3> H2N-Alk-NHRl< /RTI> (VIII) umsetzt, oder c) ein Phosphinsäurehalogenid der Formel XII
EMI54.3
where Hal halogen means, with amine connection formula Py-NH-R2 (IVa) converts, and, if desired, a received enthalogeniert bond of the formula I, in which the remainder contains Py halogen, or a received exchanges bond of the formula I, where the remainder is Py in 2 and 6-Stellung by halogen substituted, the halogen in 2-Stellung by if necessary substituted Amino, and/or if desired, a received converts bond into another bond of the invention, and/or, if desired, a received cousin into an acidic addition salt or a received salt transfers into the free cousin or into another acidic addition salt, and/or, if desired, a received mixture of isomers in individual isomers isolates.